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ENDOMETRIOSIS*

Two Hundred Cases Considered from the Viewpoint of the Practitioner

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ENDOMETRIOSIS is a frequent, not a rare, disease. In a recent test period, controlled to the extent that during it all the clinic's operations were done by one operator, there were among the female patients 78 cases of acute appendicitis and 107 cases of microscopically verified endometriosis.

The natural course of this disease is from various stages of severe pain through dyspareunia and sterility, with all the marital disharmonies attendant on those complications, to pelvic invalidism. Endometriosis, however, is one of the few diseases with proportionately serious results for which there is a specific treatment—castration. Less radical therapy is effective if the diagnosis is made even moderately early.

Unfortunately the diagnosis is oftener missed than made. Of the last 200 patients in this clinic with external endometriosis,—to which this paper is limited,—most of whom had previously been examined by one or more physicians and several of whom had been explored, only 6 entered with a diagnosis of endometriosis. No other disease of comparable frequency and severity has had, in our own experience, so low a diagnostic index. Yet the means of diagnosis are at hand. Endometriosis has a cardinal symptom, a pathognomonic sign and an unmistakable gross appearance. Also, it occurs in a sharply limited group of the population.

The missed diagnosis is not a phenomenon peculiar to New England. Nor is it the fault of the practitioner. Despite the excellent reports on endometriosis, we have found no definite description of what we believe to be its fundamental clinical syndrome. Furthermore, there is a widespread assumption that the condition is the private property of the gynecologist. This is unfortunate because endometriosis, like pregnancy, is encountered by all physicians.

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PATHOLOGY

External endometriosis is a growth of endometrium anywhere except where it belongs, in the lining of the uterine cavity; the word "growth" should be emphasized. Endometriosis closely resembles cancer. The cells are more differentiated, but it has the clinical attributes of cancer—speedy growth, spread, invasion and metastasis. Cytologically it is benign; otherwise it is cancer, but a cancer against which there is a specific treatment.

This growth, being endometrium, menstruates. The usual structural unit is an endometrial-walled cyst that menstruates into its own lumen. When the menstrual fluid meets peritoneum, it causes local chemical peritonitis. The cyst wall itself, growing centrifugally, invades the host. Invasion is opposed by growth of fibrous tissue varying in degree with the host.

When the growth occurs in an ovary there is least fibrous counterattack; the cyst enlarges rapidly and tends to perforate because it presumably becomes distended with each period. Blowout can occur, usually immediately before or early in menstruation, and produces a syndrome varying in intensity from that of mild appendicitis to that of ruptured tubal pregnancy. Seepage, as opposed to blowout, for the most part causes only an unusually painful period. Seeping menstrual fluid plasters the ovary first to the broad ligament and later to any contiguous area, with characteristic dense, cancerlike adhesions. Month after month, swellings, new seepages and new adhesions build up the so-called "chocolate cyst" of the usual illustration. It is unfortunate that so advanced a stage is the trademark of the disease. Earlier lesions are recognizable (Fig. 1).

In addition to the ovary, the pelvic peritoneum, visceral or parietal, is invaded either directly or by the droppings from an ovarian endometrioma. Here the lesion eventually becomes a so-called "blueberry spot" (Figs. 2 and 3).

The blueberry spot ordinarily does not exceed a few millimeters, but the surrounding fibrosis may be 1 or 2 cm. in diameter. The fibrosis spreads both in the host tissue and, through adhesion, to adjacent tissues. Octopuslike tentacles of endometrial tissue invade the fibrosis, and the lesion shows radiating stellate lines of contraction as if pulling neighboring tissues toward itself.

Figure 3, which shows endometriotic adhesions compared with those of chronic pelvic inflammation, demonstrates the difference between the thin, sheetlike, stretching adhesions of old inflammatory disease and the solid, stellate, puckering tentacles of active endometriosis. The adhesion of the inflammation, a protective mechanism whose work is done, yields to environment and weakens and stretches. The new growth invades the environs, clawing them to itself.

Blueberry spots tend to occur in groups, to coalesce and, with their fibrosis, to build up the cancerlike nodules that are the pathognomonic sign of endometriosis. Such conglomerate tumors cause extensive distortion or, in the sigmoid, stricture.

The densely adherent tumors and the intestinal involvement of late endometriosis may cause unusual difficulty for the surgeon and consequent danger for the patient. Despite the fact that all endometriosis, with the possible exception of that in more advanced sigmoidal strictures,[1] regresses after removal of the ovaries, merely reaching the ovaries to remove them may be dangerously difficult. It is fair to say that endometriosis is a disease that progresses at variable rates but in the direction of death until arrested by the menopause.

We have begun to recognize what we believe to be earlier forms of endometriosis than any of those described above. There are also less frequent forms, such as endosalpingiosis[2] and the debatable lesions described by Goodall,[3] all of which are beyond the scope of this paper.

Endometriosis may appear in the appendix, appendix stumps, laparotomy scars, the cervix, the bladder mucosa, the vaginal wall, along the ureter, hernial sacs, the groin, the vulva, the umbilicus, the small intestine, the abdominal and mediastinal lymph nodes and probably the lung, biceps muscle and forearm.

Internal endometriosis (adenomyosis, adenomyoma) is probably a different disease.

Diagnosis

Endometriosis tends to occur in childless women, in whom pelvic symptoms are likely to be ascribed to neurosis. The variety of places in which lesions occur and the triple action of the disease (as neoplasm, chemical irritant and presumptive hormone manufacturer) make almost any symptom possible. Also, endometriosis often accompanies other symptom-producing pelvic diseases, especially fibroids. A basic syndrome, however, can probably be identified in spite of all the adventitious symptoms. The picture has three parts: a cardinal symptom, a pathognomonic sign and a specialized susceptibility.

Cardinal Symptom

In our experience increasing dysmenorrhea is almost always present, provided the disease causes any symptoms. One hesitates to call the pain dysmenorrhea, which suggests cramps. This pain may be a cramp but it may also be an ache in the left lower quadrant, an acute stab near the appendix, a soreness in the rectum or a discomfort in the back. It may be sharply localized, or it may radiate to the sacrum or thigh. The nature and location of the pain are not important. What is significant is its relation to menstruation. This relation may vary: usually, the pain and the period are synchronous, but occasionally the pain precedes or follows the period; in 1 patient the pain accompanied ovulation rather than flow.

Of course, many lesions cause dysmenorrhea. The criterion of endometriotic pain is *increase*. Increasing dysmenorrhea is not the same as acquired dysmenorrhea. The pain of endometriosis may be acquired — that is, it may start after previously painless periods. Or it may be an increase of existing pain. In either event the increase continues and cumulates. Eventually pains meet across the month, and there is no longer intermenstrual remission but only menstrual exacerbation. Contrariwise, the pain of old pelvic inflammation may decrease at menstruation, possibly from hyperemia.

The severity of the pain is no index of the extent of the lesion. One of the puzzles of the disease is the patient with severe pain but slight lesion, or vice versa. By and large, the pain is more consistent with peritoneal lesions than with those limited to the ovaries. The likeliest to escape diagnosis is the endometrioma that slowly builds up within an ovary, without seepage and without peritoneal implant, and bursts without warning. One should be wary of appendicitis that occurs on the day preceding menstruation.

What proportion of patients who have increasing dysmenorrhea do not have endometriosis? Unfortunately the clinic lacks a symptom index, so that the answer cannot be given in numbers. Our impression is that the fraction is small.

The history of increasing dysmenorrhea probably bears some relation to the pessimism of many authors about diagnosis. Although appraised as the chief and characteristic symptom of the disease as early as 1929 by King and Fiddes,[4] its significance has remained relatively unrecognized: in two hundred articles reviewed, increasing dysmenorrhea was emphasized in twelve, mentioned passingly as one of the possible symptoms in seventeen and omitted altogether in the remainder. Before we appreciated this symptom only 20 per cent of our cases were diagnosed before operation; at present

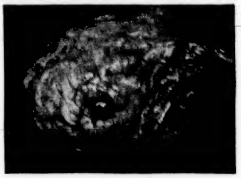
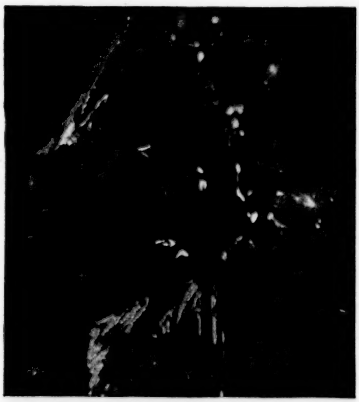


FIGURE 1. *Photograph of Ovary (x 1).*

An early chocolate cyst, 4 mm. in diameter, illustrates the importance of **visual** *exploration of the pelvis. Cysts less than 1 mm. in diameter can be identified — if one looks instead of feels.*

FIGURE 2. *Photograph of Piece of Excised Pelvic Peritoneum (x ¾).*

This shows, below, a small "blueberry spot" and, above, "red roughening."



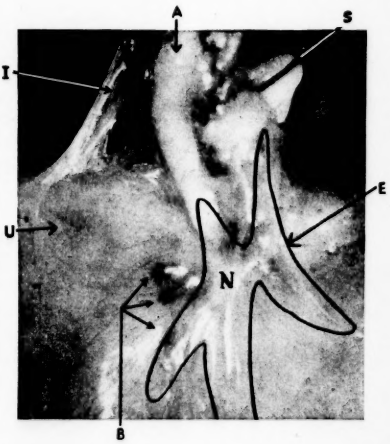


FIGURE 3. *Photograph of Both Inflammatory and Endometriotic Adhesions between an Appendix Epiploicum and the Uterus (x 2).*

U *is the uterus,* A *an appendix epiploicum, and* S *a retracting suture. This illustrates certain differences in appearance and in nature between endometriosis and chronic pelvic inflammation. The inflammatory lesion* (I) *is thin, sheet-like, stretching. The adhesion of endometriosis* (E) *is strong, solid, contracting; note the typical stellate lines of puckering. "Blueberry spots" appear at* B, *and the endometriotic nodule at* N.

70 per cent are so diagnosed, and the missed 30 per cent consists principally of patients with painless ovarian endometriomas or with early endometriosis discovered at operation for other disease or of patients who, for one reason or another, were admitted directly to the hospital without passing through the clinic. There are lessons in this last group: they were admitted by a member of the house staff; the interview with a member of the clinic was — in war days — brief; and the endometriosis was recognized for the first time at operation.

A change in the time or amount of menstrual flow is also a symptom of endometriosis. Often — and from our experience, we believe, erroneously — it is called the chief symptom. In this series it was present in a third and absent in two thirds of the cases. It is therefore of no diagnostic value. The symptom may help, however, by bringing to the physician patients who recognize irregularity as pathologic but who accept periodic pain as woman's normal lot. In every case of menorrhagia, therefore, inquiry should be made regarding dysmenorrhea.

Jarring of the pelvis, from walking on a hard sidewalk, riding on a rough road, coitus, defecation or even sitting down suddenly, may increase the pain of endometriosis. The absence of this symptom means nothing. Its presence, which connotes some serious pelvic peritoneal irritation, always suggests but is not diagnostic of endometriosis. Like menorrhagia, however, this variation may cause women who accept so-called "normal dysmenorrhea" in silence to consult a physician.

Pathognomonic Sign

Pain on movement of the cervix at vaginal examination has the same pathologic significance as the pain on jarring referred to above — that is, it signifies a serious variety of peritoneal irritation; it is also frequently present but is not pathognomonic. The pathognomonic sign is the hard, fixed, invading nodule of endometriosis. The characteristic feel of this structure is a matter of tactile memory and not to be learned from print, although if one's tactile imagination is active, Figure 3 will suggest how it ought to feel. It is nearest like the feel of cancer metastases, and to the extent that it cannot always be differentiated from these it is not pathognomonic; usually, however, it can be differentiated, and then it is definitive. Certain stratagems are useful in the search for the nodules. Rectal palpation is often more rewarding than vaginal, and combined, simultaneous rectal and vaginal examination is more satisfactory than either alone. The posterior-vault peritoneum and the uterosacral ligaments, on whose anterior reaches many of the nodules occur, can be tensed for better palpation by pushing the cervix forward by the finger or pulling it downward by a tenaculum. Examination midway between periods, followed by re-examination at the beginning of the next period, may show the nodule to be tenderer on the second occasion.

Unfortunately, nodules large enough to be palpable often indicate advanced disease, and nodules may be present but out of reach. Actually, pelvic examination substantially contributed to diagnosis in a little less than half of our cases in which the diagnosis was made. Despite a pelvis normal to palpation, therefore, the diagnosis should be made from the history alone.

Specialized Susceptibility

The occurrence of endometriosis is largely limited to one group of people. The diagnosis should not be rejected because a patient is outside this group, but the possibility should be considered in every patient within it. This group consists of women who are not having children — the sexually dormant, whether married or single.

It is often said that endometriosis causes sterility. It is true that women with advanced endometriosis are and those with early endometriosis may be sterile. Yet at least 26 cases of coexistent pregnancy and endometriosis have been collected,[5] and this series adds a probable 10: in 2 cases old endometriosis was shown at operation soon after miscarriage, 1 patient had a ruptured tubal pregnancy and old endometriosis and 7 patients had become pregnant since the estimated onset of the disease. Parenthetically, in these 7 the pregnancies seemed temporarily to have arrested the endometriosis.

That endometriosis causes sterility is true but is not the point. The significant fact is that endometriosis occurs in women of child-bearing age who are not having children. The phrase "child-bearing age" should be clarified. The youngest patient of whom we have found record was a thirteen-year-old girl in this series. There were also 1 girl of sixteen and 7 of seventeen, eighteen or nineteen years of age.[6] At the other extreme were 3 women of forty-seven to fifty and 1 of fifty-three years of age. All were menstruating, and all, except 2, had been menstruating for at least five years. Shortly after the menopause, endometriosis becomes a relic — 3 patients, ranging in age from fifty-three to sixty-six years, had inactive residua of the disease. To analyze the phrase "are not having children": in this series over two thirds of the 200 women had never had a child. This, of course, is significant. Women with children, however, can have endometriosis, — 59 of the 200 patients did, — as can the mother of a large family — 13 of these mothers had five children or more. The phrase therefore signifies only women who have not had a baby recently — that is, for about five years. In this series there were 14 women who had been pregnant within the five years before discovery of the disease. But 4 of them had artificial endometriosis, caused by operation. In 2 of the 10 patients with spontaneous disease the endometriosis appeared to have started within five years

of delivery. But in each of the other 8 the symptoms of endometriosis, we believed, could be traced back to a fallow period of five years preceding the last pregnancy. In other words, of a total of 190 patients with spontaneous endometriosis — the 10 with artificial disease being subtracted from the total of 200 — the disease seemed to have begun within five years of confinement in only 2 cases.

There is contributory evidence in the thirteen mothers who had five or more children. These women all married young, had their babies early, stopped having babies and, after five years or more, developed endometriosis. Finally, although endometriosis occurs in youth, reports of its appearance before approximately five years of menstrual life are extremely rare.[6]

The most practical item in diagnosis after increasing dysmenorrhea is therefore considered to be a history of about five years of nonpregnancy preceding the disease. And it seems to make no difference whether the nonpregnancy is from inability, indecision or lack of opportunity. Palpable endometriomas confirm the diagnosis but are absent as often as present.

Treatment

Endometriosis is a disease for which a true specific treatment is available. Following ovarian deactivation endometriosis gradually regresses, with insignificant residua. But the price — castration — is high. In the hope of avoiding castration in advanced cases, we have begun to study temporary ovarian deactivation by small doses of radium after confirmation of diagnosis by peritoneoscopic biopsy. Masculinizing, follicular and luteinizing hormones have also been suggested, but the last two are probably as likely to harm as to help.

For such a chemical problem the future may offer a chemical solution that will restrict the surgeon to the taking of biopsies. But today he has a procedure that is reasonably efficient and less costly than castration. This consists in diagnosis while all lesions are young enough to be removed individually without castration and in prophylaxis.

The arbitrary five fallow years discussed above may be new, but there is nothing original about the concept of endometriosis as a disease of the sexually dormant.[7, 8] Meigs[9] calls it a physiologic response to an abnormally uninterrupted menstrual career. If the theory is sound the prophylactic is obvious — more obstetrics would engender less gynecology. Marriage at the age of seventeen and a child every three years would probably abolish endometriosis. It should be remembered that the disease itself, not eugenics, ethics or even common sense, is under consideration. Marriage at twenty and no five years without a baby would perhaps be more sensible.

An excellent opportunity for prophylaxis is offered the practitioner when he refers to the surgeon a woman with appendicitis. Because of the frequency of endometriosis and of other unsuspected pelvic lesions, we believe that it is often fitting for the practitioner to suggest exploration of the pelvis in addition to removal of the appendix. Digital examination can miss an early lesion. But to the eye endometriosis is as unmistakable as chicken pox, so that no pelvis can be said to have been adequately investigated until it has been explored by vision. This necessitates a median incision, which, when routinely used for appendectomy in women, has revealed a surprising amount of endometriosis.

In patients with severe dysmenorrhea, even if the symptom is not increasing, exploration is often indicated when lesser treatment fails. If no endometriosis is found, presacral sympathectomy may justify the operation. Endometriosis, which is frequent and painful, causes sterility; it is therefore sound prophylaxis to be radical about deciding to explore in suspicious cases.

Some experienced operators do not bother to excise small lesions; others allow even large lesions to remain but resect three quarters or more of the ovarian tissue in the hope of diminishing ovarian function. To us, both these procedures seem overconservative, for the following reasons: large endometriomas grow from small ones; patients with small lesions may have a great deal of pain, which ceases after removal of the lesions; subtotal oophorectomy, like subtotal thyroidectomy, is a physiologic compromise; and, finally, in several cases, we have observed endometriomas that continued to grow after previous operation or the disease itself had destroyed all but a shell of ovarian tissue.

True conservatism, we believe, consists in spending an hour picking nodules out of a pelvis, even though castration could be done in ten minutes. We have set ourselves the alternative of complete extirpation or castration, and have taken pains and accepted risks to excise the disease whenever excision was possible. One of the 2 deaths in the series occurred from operation for endometriosis, the other from hepatic carcinoma metastatic from the colon in a patient whose incidental endometriosis had not been treated. The few exceptions to the rule were in young girls with extensive lesions in whom the treatment consisted in removal of all the disease that it was mechanically practicable to remove, combined with temporary castration by a small dose of radium. Obviously, the risk of radiating ova that subsequently might become impregnated should be taken only in extreme circumstances.

About half the patients in this series were castrated. To our great disappointment and despite definite improvement in diagnosis and steadily increasing willingness to resect more difficult lesions, the proportion of patients castrated is not significantly lessening. Of the first 100 patients in the series, 52, and of the last 100, 45 were castrated.

All patients in the series are being followed, but end results of treatment for endometriosis should not be quoted before the menopause. Among the castrated patients, recurrence from the use of stilbestrol has been encountered and has so far yielded to withdrawal of the medication. It can be said that radical excision without castration may afford long relief and sometimes results in pregnancy — Payne[10] reported 10 and Haydon[8] 19 patients who became pregnant following operation; Counseller[11] reported ten pregnancies in 7 patients, and 3 of our patients have had one child each.

Recurrence is suspected in 2 of our patients, who are nevertheless being only watched. The 3 patients with recognized recurrences became asymptomatic following irradiation. As Pemberton[12] has pointed out, irradiation is not to be undertaken casually. The dense adhesions of the disease may bind intestine into a dangerously immobile target for the x-rays.

Summary

Endometriosis is a progressive, painful, sterilizing, crippling disease that can be both prevented and cured. Opportunities for prevention and cure are lost because no accurate clinical picture has become generally accepted and because the frequency of the disease is not appreciated.

In the female patients seen in this clinic the incidence of endometriosis was greater than that of acute appendicitis.

Endometriosis is an antivenereal disease — that is, it is associated with sexual unfulfillment. The prophylaxis seems to be early marriage and a child every few years.

Endometriosis is a new growth of menstruating endometrium that, invading and sometimes metastasizing, tends to spread through the pelvis, causing chemical peritonitis, dense adhesions, sterility, destruction of ovaries and stricture of the pelvic intestine. Ovarian hormone is necessary to the progress of the disease. The course, which is reversed by ovarian deactivation, may be arrested by excision of the lesions. To arrest without castration necessitates diagnosis before the lesions have become mechanically unresectable.

Contrary to general opinion, clinical diagnosis is usually possible. It depends on ability to separate from a mass of adventitious pelvic symptoms and signs the following basic syndrome of endometriosis: cumulatively *increasing* pain at the time of the period occurring after about five years of menstruation without pregnancy. Endometriotic nodules are pathognomonic but often not large enough to be felt, in which event the diagnosis should be made on the basis of the history alone.

Because endometriosis can be seen long before it can be felt the practitioner should be as radical about advising surgical exploration as the surgeon is conservative about castration.

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BRIGHT'S DISEASE: CLINICAL MANIFESTATIONS IN RELATION TO ETIOLOGY AND PROGNOSIS*

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ROCHESTER, MINNESOTA

IN 1827 Bright[1] pointed out the association between dropsy, albuminuria and hardened kidneys. In this simple correlation he established the foundation for a multitude of observations that accumulated in succeeding years under the caption of "Bright's disease." It soon became apparent that, from both a clinical and a pathological standpoint, Bright's disease was not an entity but an assemblage of diseases. Subsequent efforts to achieve specificity resulted in many classifications, some accurate and many detailed. But what is satisfying to an expert in the field is not always expedient for one whose circumstances demand familiarity with the range of clinical medicine. As a result, physicians have frequently resorted to the broad and time-honored diagnosis of Bright's disease rather than attempting to drag out a rarely recognized term buried deep in some current classification of vasculorenal disease.

But Bright's disease is not a satisfying diagnosis. Between excess of generalization and impracticable specificity there should be some compromise. A simple classification of vasculorenal disease from the point of view of a clinician should be one in which the nomenclature is descriptive of clinical findings. It need not become involved with pathological terms such as "small granular kidneys," "large pale kidneys," "primarily and secondarily contracted kidneys" and "flea-bitten kidneys."

FUNDAMENTAL CLINICAL MANIFESTATIONS

The important clinical findings in Bright's disease ("vasculorenal disease" is an equally comprehensive and more descriptive term) are renal insufficiency, dropsy and hypertension. If, in a scheme of diagnosis, importance is to be attached to these clinical manifestations, it is essential that the character of each be understood. For this reason the following elaboration of the nature of each is undertaken.

Renal Insufficiency

It is apparent that one of the most significant effects of disease on the kidney is impairment of functional capacity. The degrees of damage may be described under three headings: latent renal damage, compensated renal insufficiency and uncompensated renal insufficiency.

Latent renal damage. The existence of latent impairment of kidney function is dependent on the large reserve capacity of the normal organ. Under this heading are included cases in which there is no demonstrable reduction in the functional capacity of the kidney. Responses to all tests are within the normal range. Yet a pathologic process known to affect the kidney exists. An example of this type of renal damage is found in early essential hypertension.

Compensated renal insufficiency. At this stage of renal damage, a sufficient proportion of the functioning elements of the kidney have been damaged or destroyed to eliminate a large measure of the reserve capacity of the organ. So long as the patient is in good general health, the concentration of urea in the blood remains normal. There is a reduction, however, in the capacity of the kidney to do a specific amount of work in a limited time, as demonstrated by the urea-clearance test. The power to produce a concentrated or a dilute urine is impaired. With the development of an unusual strain on the organ, actual renal insufficiency develops and the concentration of blood urea may rise.

Uncompensated renal insufficiency. With the development of this degree of destruction of kidney substance, not only are the reserves of the organ exhausted but also the capacity to care for the current excretory load is lost. The concentration of urea in the blood is elevated and, unless compensation is restored, mounts steadily. The end result of this sequence is the development of the uremic state. The term "uremia" or "uremic state" may well be reserved to describe that terminal phase of renal insufficiency during which certain overt manifestations of kidney failure develop — namely, somnolence, confusion, nausea, vomiting, muscular irritability and convulsive seizures.

Dropsy

In the absence of cardiac failure, dropsy in a case of chronic renal disease is the outward and visible sign of a derangement in the metabolic processes of the body that has been designated the "nephrotic state." The initial factor in the development of this syndrome is probably the loss of excessive amounts of albumin in the urine. The albuminuria itself is believed to be secondary to increased permeability of the glomerular membranes, permitting the smaller molecules of the normally retained serum proteins to pass into the urine. Secondary to the

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loss of serum proteins there develops hypoproteinemia associated with a disturbance in the osmotic equilibriums of the blood and tissue fluids, culminating in the accumulation of increased amounts of fluid in the tissue spaces. The hyperlipemia that is also a feature of the nephrotic syndrome is probably a compensatory reaction directed toward restoration of a more nearly normal osmotic relation.

Hypertension

Of the three major clinical manifestations of vasculorenal disease, elevation of the blood pressure is the most frequent. Foregoing for the moment any distinction between angiospastic processes and the more usual sclerosis and narrowing of the arterioles, one may divide the hypertensive reaction of vasculorenal disease into four groups, according to the classification of Keith, Wagener and Barker,[2] in which certain changes in the ocular fundi are of fundamental importance. The divisions are as follows:

Group 1. Patients who have only mild narrowing or sclerosis of the retinal arterioles fall into this division.

Group 2. Patients are placed in this category if they have moderate to marked sclerosis of the retinal arterioles, whether of the chronic type — characterized especially by exaggeration of the arterial reflex and arteriovenous compression — or of the postangiospastic type — characterized especially by generalized and localized irregular narrowing of the arterioles.

Group 3. Patients who have retinitis of the angiospastic type — characterized especially by edema, cotton-wool patches and hemorrhages in the retina, superimposed on a combination of sclerotic and spastic lesions in the arterioles — belong to this group.

Group 4. This group comprises patients with measurable edema of the disks in addition to the findings described above.

Although the arteriolar changes are readily studied clinically only in the retina, pathological investigations support the postulate that the arteriolar disease in hypertension is generalized.[3–5] Therefore, in cases of hypertension, an accurate descriptive diagnosis is "diffuse arteriolar disease with hypertension, Group 1, 2, 3 or 4."

Etiology

Regardless of the nature of the specific disease affecting the vasculorenal system, the major clinical manifestations may be described with reasonable consistency in terms of the triad discussed above. To this proposition there is a corollary: Bright's disease is not an entity but an assemblage of diseases grouped together, not because of similarity of cause but because of similarity of effect. In the following paragraphs the relation between certain specific causes and the triad of effects is elaborated, Bright's disease being analyzed from the etiologic standpoint whereas the fundamental unity found in the clinical expressions is retained.

Chronic Glomerulonephritis

The term "chronic glomerulonephritis" implies the existence of an earlier phase of the disease that in some cases was acute, almost explosive. The patient so afflicted was obviously ill, with an elevated temperature and labored respirations. The urine contained many casts and erythrocytes and much albumin. Anasarca, hypertension and renal insufficiency may have been present simultaneously in this acute phase.

In contrast, this preliminary stage may have had an insidious onset unattended by symptoms. Its existence could be defined only by examination of the urine, in which there were small amounts of albumin and sometimes a few casts, erythrocytes and pus cells.

Slowly or rapidly, but fortunately not inevitably, chronic glomerulonephritis evolves from the nephritis of acute or insidious onset. The initial lesion was in the glomerulus. As the destructive changes progress in this portion of the nephron, any one or any combination of the three clinical features of vasculorenal disease may develop concurrently or sequentially. Furthermore, although two or all three manifestations may be present, one component may be mild and another severe. Finally, a patient may pass through phases during which, in succession, he suffers primarily from one aspect of the triad, he recovers from this and he succumbs to another expression of the disease.

It is not expedient or essential to clarity to present illustrations of all these potential combinations. Two examples are sufficient. First, a patient with chronic glomerulonephritis and findings pathognomonic of all phases of the triad may present the following: a blood urea concentration of 200 mg. per 100 cc. (normal 15 to 40 mg.); large amounts of albumin in the urine; a value for serum protein of 3.5 gm. per 100 cc. (normal 6 to 8 gm.), with an albumin-globulin ratio of 1.0:1.2 (normal 2.0:1.0); anasarca; and hypertension with associated arteriolar disease. A descriptive diagnosis in such a case is chronic glomerulonephritis with severe renal insufficiency (as indicated by the elevated blood urea level), nephrotic syndrome (as demonstrated by albuminuria, hypoproteinemia, reversal of the normal albumin-globulin ratio and anasarca) and superimposed diffuse arteriolar disease with hypertension.

In contrast is the patient with a relatively pure nephrotic syndrome. Typical findings in such a case are a blood urea value of 32 mg. per 100 cc.,

marked albuminuria, a concentration of serum protein of 3.5 gm. per 100 cc., with an albumin-globulin ratio of 1.0:1.2, and generalized anasarca, but with normal blood pressure and no definable narrowing or sclerosis of the retinal arterioles. Such a patient presents evidence indicative of adequate renal function and of a normal arteriolar system without hypertension in the presence of a well developed nephrotic syndrome.

As a concluding observation regarding chronic glomerulonephritis it may be noted that renal insufficiency unattended by hypertension or by the nephrotic syndrome is probably the rarest clinical manifestation of the disease. Such cases occur, however, and a patient may pass into the uremic state and die without the development of either of the other two features of the triad.[6]

Essential Hypertension

Primary consideration was given above to chronic glomerulonephritis because of its basic relation to the three cardinal manifestations of vasculorenal disease. During the course of chronic glomerulonephritis, hypertension may or may not appear and may or may not be a symptom of the disease. But hypertension may also occur as an isolated phenomenon, apparently unrelated either to chronic glomerulonephritis or to any of the other entities affecting the vasculorenal system. In this event, the clinical manifestation becomes the disease and bears a name, albeit an unrevealing one — "essential hypertension." From the standpoint of incidence alone, essential hypertension is the most important entity included under the term "Bright's disease."

Whereas the site of the initial lesion in chronic glomerulonephritis can be identified with precision, the primary change in essential hypertension remains indeterminate. The kidney undoubtedly becomes involved in advanced stages of the disease, but that the primary lesion is renal is far from an established fact. Rather, the initial lesions in essential hypertension appear to be arteriolar and so generalized as to justify the caption "diffuse arteriolar disease."

However different their origins, chronic glomerulonephritis and essential hypertension in their final stages may be confusingly similar. Although the nephrotic syndrome is peculiar to glomerulonephritis, renal insufficiency and hypertension are frequently associated in the terminal stages of both diseases. Whereas marked albuminuria with many casts and erythrocytes is usually indicative of primary glomerulonephritis, all these urinary findings may be duplicated in the terminal stages of severe hypertension. Sometimes the history or the age of the patient supplies evidence helpful in defining the initial lesion. A previous episode of acute glomerulonephritis, a record of albuminuria for years prior to the onset of hypertension and youth of the patient may suggest that the initial lesion was in the glomeruli. On the other hand, a history of high blood pressure of many years' duration, without other indications of impaired health, is more suggestive of primary hypertensive disease. In some cases it remains for the pathologist to establish whether the primary lesion was arteriolar or glomerular, but the decision is not always achieved with finality even at this ultimate stage.

Other Conditions

A sound knowledge of chronic glomerulonephritis and essential hypertension and their interrelations is fundamental to an understanding of the rarer and often simpler causes of Bright's disease. One of these is chronic pyelonephritis, in which extensive destruction of renal tissue by an infectious process may lead eventually to advanced renal insufficiency with superimposed diffuse arteriolar disease and hypertension. In polycystic disease, destruction of the renal parenchyma is accomplished by a different means but with similar results. Toxic processes may lead to tubular damage and suppression of formation of urine, with consequent acute renal insufficiency usually unassociated with appreciable hypertension or the nephrotic state. Lymphoblastomatous or amyloid infiltrations of the kidney may give rise to a relatively pure nephrotic syndrome later complicated by renal insufficiency. Periarteritis nodosa is sometimes attended by hypertension and ultimately by renal insufficiency. But whatever the pathogenesis of the lesion in the vasculorenal system, the overt expressions of the disease can be related in most cases to one or more of the well established patterns.

Prognosis

In concluding this survey it is reasonable to turn from the consideration of diagnosis and classification to the problems of prognosis and treatment, in which the delineation of the triad of renal insufficiency, nephrotic syndrome and hypertension is also of value. Prognosis is not a precise science and demands calculations more subtle than those of arithmetic. Some insight into the future of the patient with vasculorenal disease can be achieved, however, if it is recognized that the course is dependent on the number of the clinical manifestations that are combined, as well as on the severity of the individual components. This generalization is applicable to the more frequent etiologic processes in vasculorenal disease — namely, chronic glomerulonephritis, essential hypertension and chronic pyelonephritis. The significance of the generalization is minimized in cases in which the primary process is one of the rarer entities, such as lymphoblastoma, amyloid disease or periarteritis nodosa.

In illustration, comparison may be made of chronic glomerulonephritis in 2 patients of similar

age in whom the illness has been present for a similar period. Each has renal insufficiency with a blood urea concentration of 150 mg. per 100 cc. But one has superimposed diffuse arteriolar disease with hypertension, Group 3, whereas the other has an essentially normal arteriolar system. The prognosis for the latter is much better than that for the former.

Equally significant is the consideration of 2 patients each with a moderately severe nephrotic syndrome. One has normal renal function so far as can be determined by tests, and the other has uncompensated renal insufficiency. All else being equal, the prognosis for the latter is less favorable than that for the former, not only because two pathologic processes are worse than one but also because treatment of one manifestation often entails application of measures unfavorable to the other. The patient with renal insufficiency has lost his ability to produce a concentrated urine. Therefore he must excrete large amounts of urine to avert a rise in the blood urea concentration. But the wisdom and the feasibility of administering large amounts of fluid to the patient with an advanced nephrotic syndrome constitute problems that evade simple resolution.

* * *

More extended consideration of therapeutic problems in cases of Bright's disease is not appropriate to this limited discussion. If there is value in undertaking the treatment of vasculorenal disease by application of measures directed toward alleviation of renal insufficiency, the nephrotic syndrome or hypertension, that value is apparent in the illustrations elaborated above.

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HEPATIC COMPLICATIONS OF AMEBIASIS*

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THE purpose of this paper is to invite attention to some of the bizarre and puzzling manifestations of amebiasis that have been encountered, with special reference to hepatic complications. Pitfalls in diagnosis may be easily avoided if the possibility of amebiasis is kept in mind. It should be remembered that dysentery is an infrequent manifestation of amebiasis. Even lesions in the large intestine are not invariably found on sigmoidoscopic examination. Therefore, despite the absence of a history of dysentery, amebiasis must be considered in the differential diagnosis of many bizarre clinical syndromes.

The disease is not restricted by geography or climate. Poor sanitation and poor hygiene are chiefly responsible for its spread. It is frequent in the southern states but is not rare in the northern ones. In 1933 the disease intruded itself into the national consciousness as a result of the outbreak of amebic dysentery at the Century of Progress Exposition in Chicago. At present, a far more serious source of dissemination has appeared: in our work at this large hospital we are seeing ever-increasing numbers of returning service men affected with tropical diseases. Bomford,[1] in an article on chronic amebiasis in soldiers of the British Army, emphasizes the fact that awareness of this disease and its many manifestations results not only in early diagnosis but also in a reduction of the hazards of dissemination. In 1942 Faust[2] estimated the incidence of carriers to be 20 per cent of the total population. What effect the recent influx of a host of carriers will have on this already menacing number time alone will tell. In the Veterans Administration hospitals physicians are in a particularly favorable position to observe this disease and to check its spread by prompt diagnosis and adequate treatment. The large number of veterans of World War II who will pass through these hospitals within the succeeding months and years constitutes a challenge to the efficiency of the medical profession. The future will clearly show how effective the fight against amebiasis has been. A high index of suspicion is the keynote of early diagnosis.

The morphology of the parasite is well known, but differentiation of this pathogenic ameba from normal nonpathogenic inhabitants of the human intestinal tract is difficult. The motile vegetative forms or trophozoites, which are invasive and are responsible for the pathologic changes characteristic of the disease, do not serve as a means of transmission. They are short lived outside the body and probably cannot survive passage through the stomach following ingestion of contaminated food. The cysts are the infecting agents, because they are resistant to marked changes in their environment. It is essential to realize that ordinary chlorination does not destroy the encysted forms, which at freezing temperatures can remain viable for weeks. The character of the stools determines the form of the parasites present. In the presence of diarrhea, it is exceptional to find anything but trophozoites. If the formed stools are passed, only cysts are usually found. Needless to say, careful stool examinations by experienced technicians are helpful in the diagnosis. It is reiterated, however, that the absence of the pathogen from the stools is not positive evidence that amebic infection is not present. Sigmoidoscopy should always be performed because the diagnosis of amebic colitis is frequently made from the gross appearance of the colonic ulcers, and in addition, the organism is often found in smears taken from the floor of these ulcers. It is not the purpose of this paper to outline diagnostic procedures, which are covered in standard texts.

Invasion of the submucosa of the wall of the colon may be followed by the entry of *Endamoeba histolytica* into radicles of the portal vein and metastasis of the infection to the liver. This is followed by amebic hepatitis or amebic abscess. Such abscesses may be single or multiple, acute or chronic. In an analysis of 1000 cases of amebic dysentery Payne[3] found hepatitis to be present in over 50 per cent and liver abscess in almost 3 per cent; the latter figure is in close agreement with that of other investigators — Craig[4] observed liver abscesses in 5 per cent of 745 cases. The term "amebic hepatitis" is used to indicate the early phase of amebic hepatic disease before frank abscess can be diagnosed. Ochsner and DeBakey[5] emphasize the differentiation of the two. Sodeman and Lewis[6] stress the fact that it is impossible to be certain clinically that small single or multiple abscesses are not present during the early phase, when diagnosis and treatment are extremely important.

Multiple foci of necrosis may coalesce to form a single large abscess. Leukocytic infiltration of the wall occurs even in the absence of secondary bacterial infection. The most frequent seat of the

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abscess is the upper and posterior portion of the right lobe.[4] Abscesses in this lobe often extend upward and may penetrate the diaphragm and rupture into the lung. It is well known that amebic abscesses occur in many other organs.

Hepatic disease complicating amebiasis usually appears one to three months after an attack of dysentery, but it may manifest itself during an attack or much later. The symptoms of hepatic abscess include pain or discomfort over the liver, with occasional reference to the right shoulder, irregular and intermittent fever, sweats, chills, nausea, vomiting, weakness and loss of weight. Jaundice, except in mild degree, is unusual. Diarrhea or dysentery is present in only about a fourth of the cases of proved liver disease. The diagnosis of hepatic amebiasis depends primarily on a high index of suspicion. Not infrequently a diagnosis of fever of undetermined origin is carried for weeks, because the clinical picture is not specific and the physician does not consider amebiasis as a possible cause of the symptoms. Liver-function studies are not diagnostic; they are merely suggestive and help to point the finger of suspicion at the liver. Leukocytosis of moderate degree is usually present. Stool examination for amebic cysts is, of course, of paramount importance, but is often negative even in the most competent hands. The use of intravenous Diodrast and planography is advocated in attempting to locate a liver abscess. Because of its specificity in amebiasis, emetine constitutes a therapeutic test of great value, but since the drug is a potent protoplasmic poison, it should be used circumspectly.

The following case reports are presented to illustrate the hepatic complications of amebiasis, as well as the extreme difficulty of diagnosis. Because of the obscure nature of the disease it is easy to see how errors in treatment can occur unless one is constantly aware of the possible existence of amebiasis.

Case 1. R.C.D., a 35-year-old man, was admitted to the hospital, on October 18, 1945, for the treatment of malaria. The significant fact in the history was service in the Southwest Pacific area, during which he had had malaria and amebic dysentery. Prior to this admission he had suffered from diarrhea and pain in the left upper quadrant of the abdomen, accompanied by chills, fever and sweats.

Physical examination on admission revealed the patient to be acutely ill. The only significant finding was marked tenderness and muscle spasm in the left upper quadrant of the abdomen, with no definite splenomegaly. The temperature was 102°F., the pulse 100, and the respirations 22. Examination of the blood showed a red-cell count of 4,010,000, with a hemoglobin of 86 per cent (Sahli), and a white-cell count of 13,000, with 81 per cent neutrophils. No malarial parasites were found in the blood smear.

The patient was placed on a regimen of quinacrine, which had no effect on the clinical course — the patient suffered from fever, chills and sweats at irregular periods, with weakness and occasional nausea and vomiting. The tenderness and pain in the left upper quadrant persisted. The red-cell count gradually diminished, and a transfusion of 500 cc. of whole blood was given on three occasions. Examination of the stools revealed no amebic cysts or motile forms. Sigmoidoscopic examination was negative. The cephalin-flocculation test was +, and the icterus index was 9 and 3 on two occasions. A gastrointestinal x-ray series was negative. A sense of fullness developed in the epigastrium, together with slight enlargement of the liver. At the same time the patient's sense of well being gradually improved, and the pain in the left upper quadrant of the abdomen slowly subsided. No splenomegaly could definitely be made out at any time.

On November 21 a definite, tender mass about the size of a lemon was noted in the left upper abdominal quadrant. Surgical exploration disclosed an encapsulated abscess in the region of the anterior surface of the left lobe of the liver. The abscess was incised, freeing "anchovy-paste" pus, drained by suction, packed and irrigated daily with 1:1000 solution of emetine hydrochloride. At the same time 20 mg. of emetine hydrochloride was administered intramuscularly three times a day for 7 days.

On November 25, while the patient's condition was slowly improving, he developed a chill, followed by a rise in temperature to 103.4°F. A blood smear revealed the presence of *Plasmodium vivax*. Response to quinacrine hydrochloride was prompt, and convalescence continued uneventfully. The patient made a complete recovery.

In the early stages of the illness the patient's chief complaint was directed entirely toward the left upper quadrant. The consistently negative blood smears and the failure to respond to quinacrine on admission removed malaria from the list of diagnostic possibilities, although this disease had appeared to be the likeliest cause of the chills and fever. Subsequently, intensive studies made to rule out the presence of blood-stream infection and renal suppuration were negative. The possibility of amebiasis had been entertained, but no definite findings were noted. In retrospect, we believe that the use of emetine early in the course of hospitalization would have been of significant diagnostic value, and might conceivably have prevented the formation of a full-blown liver abscess. Despite the failure to find the pathogen in the feces, the pus or the wall of the abscess, it was considered certain, on clinical grounds, that the patient did have an amebic abscess. The pus was characteristically free of pathogens, although they are often found in the wall of the abscess.

Case 2. W. F. B., a 27-year-old farmer, had been discharged from the Army on January 20, 1946, shortly after his return from the Southwest Pacific. At the time of discharge he was in good health. He had never been ill during his service in the Army and did not recall any minor episodes of diarrhea or fever. About 3 weeks prior to admission to the hospital he became ill, with fever and pain in the right chest. He consulted his family physician, who treated him for malaria without improvement and who, about 10 days before admission, thought that there was fluid in the right chest. No x-ray film was taken, nor was a thoracentesis performed. On admission the patient complained of mild pain in the lower right chest on deep inspiration, as well as a slight cough without expectoration. There had been no dyspnea. He had lost 15 pounds in the preceding 2 weeks. He had had frequent head colds for several years. Several chest x-ray films taken in the Army had been negative for tuberculosis. He had had no significant illness or operations.

Examination revealed a well developed and well nourished man, who was ambulant and not acutely ill. Significant findings were slight impairment of percussion resonance over the extreme right base of the chest posteriorly, distant breath sounds in the same area and occasional superficial fine rales. No friction rub could be heard. The liver edge, which was palpable on deep inspiration just under the right costal margin, was somewhat tender. Heavy fist percussion over the liver elicited pain. The temperature was 100°F., the pulse 88, and the respirations 18.

Examination of the blood disclosed a normal red-cell count and hemoglobin, with a white-cell count of 15,900 and a normal differential. No malarial parasites were found in the smear. Urinalysis showed a few white cells per high-power field. The sedimentation rate was 3 mm. in 1 hour. Repeated sputum specimens were negative for tubercle bacilli. An intradermal tuberculin test was positive. Stool examinations for ova and parasites were negative. Blood agglutination tests for typhoid, paratyphoid A and B, undulant and typhus fevers were negative. A prostatic smear revealed a few pus and epithelial cells but no bacteria.

A roentgenogram of the chest taken on February 25 showed obliteration of the right costophrenic angle probably due to fluid; the lung fields were clear. Examination was repeated on March 20, when the diaphragms were smooth in contour and the costophrenic angles were clear. Another roentgenogram, taken on April 6, disclosed clear lung fields but abnormal elevation of the right dome of the diaphragm. Intravenous and retrograde pyelography revealed no abnormalities.

The patient ran an irregular, febrile course, the temperature ranging from 98 to 102°F. almost daily. There was no response to penicillin and sulfadiazine. For 6 days, 65 mg. of emetine hydrochloride was administered intramuscularly every day, concomitantly with oral administration of Diodoquin. Within 24 hours the temperature became normal and remained so. The patient began to regain his lost weight and soon recovered his former sense of well being. The hepatic tenderness also subsided, and the liver edge was no longer palpable. At no time was any abnormality noted on sigmoidoscopic examination.

Despite the normal sigmoidoscopic findings and the failure to demonstrate *E. histolytica* in the stools, the dramatic response to emetine and Diodoquin leaves little doubt that this patient had a liver abscess due to amebic infection. It is not unusual for hepatic abscesses to incite diaphragmatitis, pleuritis and pleural effusion, and this chain of events is considered to have occurred in this case. So far as could be determined, the hepatic abscess subsided. Further observation is warranted, however, since relapses may occur, necessitating surgical drainage.

CASE 3. U. W., a 25-year-old Negro veteran of the North Burma campaign, had been discharged from the Army because of accumulated points on September 1, 1945. His health as a civilian had been good, and he had never been ill while in the service. On the day of discharge he suddenly developed severe, cramping pain in the upper abdomen, with nausea and vomiting; the stools were normal. The symptoms became progressively worse, and on September 7 he was admitted to the hospital.

On physical examination the patient was acutely ill and appeared to be in severe pain, rolling and tossing in bed. He lay with the knees flexed on the abdomen. He was perspiring freely. There was rigidity of the abdominal muscles in the upper half of the abdomen, with marked tenderness. On palpation there was a sensation of fullness in the upper abdomen. The lower abdomen was soft; no jaundice was noted. Rectal examination was negative. The temperature was 99.2°F., the pulse 100, and the respirations 20. Examination of the blood disclosed a red-cell count of 2,050,000, with a hemoglobin of 59 per cent (Sahli), and a white-cell count of 20,950, with 80 per cent neutrophils. The prothrombin time was 25 seconds (normal, 18 seconds). The total serum protein was 8.7 gm. per 100 cc., with an albumin of 3.0 and a globulin of 5.7 gm. The cephalin-flocculation test was +++. The icterus index was 5.7. A bromsulfalein test showed 10 per cent retention of the dye at 45 minutes and 5 per cent at 60 minutes. A blood smear for malaria was negative. A roentgenogram of the abdomen was negative, as was a urinalysis.

It was thought by the surgeon that an exploratory laparotomy should be done because of the possibility of a perforated duodenal ulcer. Operation disclosed an enlarged liver of firm consistence, with fine nodules on its surface. The postoperative course was uneventful except for fever and nausea. On September 22 the patient developed diarrhea and examination of the stool showed *E. histolytica*. He was placed on emetine hydrochloride, carbarsone and later Diodoquin, with prompt subsidence of the temperature and symptoms. On October 14, during convalescence, he suddenly developed chills and fever. A blood smear was positive for *P. vivax*. The white-cell count was 5600, with 60 per cent neutrophils. Quinacrine obtained prompt and satisfactory results. The patient left the hospital on October 28, fully recovered.

The pathological report was as follows:

> Histologic examination reveals a section of liver whose portal canals are infiltrated with numerous inflammatory cells, mostly round cells. Some of these are plasma cells. There is a scattering of eosinophils. Free hemorrhage is noted in the interstitial tissue. There is early connective tissue replacement, with early cirrhotic changes. No specific organism is noted in the section. There are no parasitic ova. There are some attempts at biliary regeneration. Diagnosis: hepatitis, with early cirrhotic changes.

If the possibility of amebic hepatitis had been seriously considered in this case, it is likely that surgical intervention could have been avoided. At this stage, treatment with emetine is effective and often prevents the development of large liver abscesses requiring surgical drainage. It is interesting to note that there was a well marked leukocytosis, as well as a clinical picture of an acute surgical abdomen. Even if one is aware of the possibility of acute amebic hepatitis, it is difficult to see how surgery can be withheld in some cases of this type. The therapeutic test of emetine, if time permits, is a prompt help in diagnosis. Another point of interest in this case was the absence of jaundice, despite the diffuse hepatitis.

CASE 4. V. B., a 34-year-old man, was admitted to the hospital on November 22, 1945. Five weeks previously, while returning from the Southwest Pacific, he had developed abdominal cramps and diarrhea, with blood and mucus in the stools. Two days before admission these symptoms recurred. The diarrhea soon became less marked, but anorexia and pain over the liver set in. There was no nausea or vomiting. No other significant facts were uncovered in the history.

Physical examination revealed a moderately ill but well developed and well nourished man. The abdomen was soft, flat and not tender. On deep inspiration the edge of the liver was palpable and tender. No jaundice was present. The temperature was 102.6°F. and the pulse 86. The blood pressure was 130/90. A clinical diagnosis of amebic dysentery and hepatitis was made.

Examination of the blood showed a hemoglobin of 96 per cent (Sahli) and a white-cell count of 18,100, with 83 per cent neutrophils, of which 15 per cent were nonsegmented forms. No malarial parasites were seen in a thick blood smear. The cephalin-flocculation test was +++, and the icterus index 5. On November 23 trophozoites of *E. histolytica* were identified in a stool specimen.

The temperature was remittent, reaching 104.4°F. 2 days after admission. Emetine therapy was instituted on November 23 and continued in a daily dosage of 65 mg. intramuscularly for 7 days. Diodoquin was subsequently administered for 3 weeks. The temperature subsided and reached a normal level on December 1, after which it remained normal. Symptomatic improvement was quite marked by November 28.

The patient made an uneventful recovery and was discharged from the hospital on January 17, 1946. Prior to discharge laboratory studies were repeated and revealed a normal white-cell count and differential. The cephalin-flocculation test was ++, and the bromsulfalein-retention test was normal. The icterus index was 5.8. A chest x-ray film was normal. Stool studies disclosed no pathogenic organisms.

This case provides an example of prompt diagnosis and early institution of treatment. The results were gratifying in that shortly after institution of therapy the patient showed marked improvement and proceeded to an uneventful recovery. This case illustrates the concomitance of amebic dysentery and hepatitis, probably in the preabscess stage. The early diagnosis was of course aided by the presence of diarrhea and the finding of the motile vegetative form of *E. histolytica* in the stool.

Summary

Amebiasis constitutes a challenge not only to the medical profession at large but also to the physicians of the Veterans Administration. Because of the bizarre symptomatology, the diagnosis of amebiasis is beset with many difficulties and pitfalls. The great number of potential carriers of *Endamoeba histolytica* makes the problem one of immediate importance. It is imperative that physicians be acquainted with the problem of amebiasis and be constantly on the alert to make the diagnosis early. Prompt therapy is the only method of preventing the serious and sometimes fatal complications of the disease.

Four cases of amebiasis with hepatic complications are presented, with a view to emphasizing the difficulties of diagnosis. It is anticipated that such cases will become more frequent within the next few years.

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CLINICAL NOTE

FRIEDLÄNDER-BACILLUS MENINGITIS TREATED WITH STREPTOMYCIN*

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INTEREST in the treatment of local and general infections caused by organisms ordinarily resistant to the usual antibiotics has become increasingly stimulated by recognition of the fact that within recent years isolated cases have been reported in which successful results were obtained. In 1943 Ransmeier and Major[1] reported a case of septicemia associated with Friedländer-bacillus meningitis and published the report after an analysis of 29 cases of similar type that had been collected from the literature. In the 30 cases reported so far, 3 patients recovered, 2 with the use of the sulfonamides and 1 following operative evacuation of an abscess.

Mori,[2] in 1943, reported a case of meningitis due to a Friedländer bacillus in a twenty-six-month-old infant, with recovery following sulfonamide therapy.

In February, 1945, the favorable effects of streptomycin in experimental infections with micro-organisms of the Friedländer group were reported.[3] In November of the same year Herrell and Nichols[4] discussed the clinical use of streptomycin in a study of 45 cases in which bronchiectatic involvement by the Friedländer bacillus was treated by aerosol and intramuscular injection of streptomycin.

It is apparent that, although streptomycin is being employed with increasing frequency, experience with the drug is limited. In the following case a patient with recognized meningitis due to Friedländer bacillus Type B was treated by intravenous and intrathecal injections of streptomycin. The clinical findings indicated an unmistakable, overwhelming meningitis, but evidence of such an infection was entirely absent grossly and almost so microscopically at the time of death.

Case Report

F. M., a 49-year-old married man, was admitted to the hospital on July 30, 1945, with a diagnosis of a right-frontal brain tumor.

The past history indicated that he had not felt vigorous for 25 years. Seven years before admission he had been hospitalized for 8 months at the Veterans Administration Facility at Rutland Heights, Massachusetts, because of tuberculosis, but no evidence of activity had been found. About 4 years later he began to have right-sided headache and difficulty in vision involving the right eye and to experience pins-and-needles sensations in the left hand and arm. Two and a half years before admission he had had a spell of unconsciousness during the night, and the spells had recurred at intervals of about 3 months until 5 weeks before admission; since then there had been three seizures. An aura, in the form of restlessness, was experienced preceding the convulsions. On one occasion there had been urinary incontinence. In 1944 the patient had been hospitalized at the Soldiers' Home in Chelsea, Massachusetts, at the Veterans Administration Facility, Bronx, New York, and at the Boston City Hospital. During 1945 he had been at the Veterans Administration Facility at Mt. Alto, Washington, D. C., and at the Veterans Administration Facility, Rutland Heights, Massachusetts. During these earlier periods of hospitalization two encephalograms and a ventriculogram had been done.

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On admission the patient complained of head pain and of difficulty in co-ordination of the eyes and hands. He had a feeling as though his head were being pulled to the right and backward. He was conscious of difficulty in memory and cerebrated more slowly than usual. He had also been conscious of increasing irritability during the preceding 2 months.

Physical examination showed a well developed and well nourished man 71½ inches tall and weighing 151 pounds. Two ventriculographic buttons were palpable in the skull. There was uncertainty in gait. The head intermittently and involuntarily twisted, the chin turning to the left and the occiput far to the right. There was considerable rhythmic tremor of the musculature, particularly about the shoulder muscles. The eye pupils, fields and fundi were normal. The breath sounds were harsh, but the heart sounds were normal. The pulse was 76, and the blood pressure was 124/80. Examination of the abdomen and extremities was negative, and the reflexes were physiologic.

Prior to operation the blood Wassermann and Mazzini reactions were negative. The hemoglobin was 16.9 gm. and the white-cell count was 7100. Urinalysis was negative for sugar, albumin and organized pathologic elements. The sedimentation rate was 15 mm. in 1 hour. The coagulation time was 3¾ minutes, and the bleeding time 1¼ minutes.

X-ray study on August 2 disclosed that the apex of the right lung was obscured. There was evidence of fibrosis and calcification above the level of the 2nd rib anteriorly, most marked in the extreme apex. These changes suggested parenchymal infiltration, apparently of long duration, with no evidence of recent changes. The remainder of the lung field was clear, with no changes in the cardiac silhouette. There was a slight bulge of the aortic knob. The changes in the right upper lung were suggestive of a tuberculous process. X-ray examination of the skull revealed areas with a somewhat circular appearance on both sides of the median line, apparently in the occipital region. It was impossible to state whether or not these findings were due to trephining or to bone erosion. No other abnormalities worthy of note could be made out. There was no indication of any definite lesion. The blood-vessel markings and the sutures disclosed no variations.

On August 13 a ventriculogram showed absence of filling of the anterior horn of the right ventricle. There was slight displacement of the ventricular system to the left.

On that day a craniotomy was performed by Dr. Gilbert Horrax and his associates, and a meningioma was removed from the right hemisphere in the frontal area. On the following morning the pulse, which had been under 90, had climbed to 120, the temperature was 102.2 and, later that day, 103.2° F., and the respirations were 35 per minute. From that time on until the time of death the patient ran a spiking febrile course, the temperature receding to normal only on August 18, and for the most part spiking to 103° F. The pulse and respiration were proportionately elevated. On the 3rd hospital day the patient complained of soreness on swallowing. Three days later he complained of a sore throat and a small grayish membrane was observed in the right tonsillar fossa. A throat culture was reported as showing the following organisms: gram-positive, lancet-shaped diplococci, with the appearance of pneumococci; short-chain, nonhemolytic streptococci; staphylococci; and gram-negative, encapsulated diplobacilli, with the appearance of Friedländer bacilli.

On August 20 lumbar puncture was done and 15 cm. of xanthochromic fluid was removed under pressure. On the following day the patient was noted to be less alert; he was hypersensitive to touch and less rational. On that day 20 cc. of definitely cloudy fluid was removed that contained 100 white cells and 5 red cells per cubic millimeter and had a sugar content of 16 mg. and a protein content of 136 mg. per 100 cc. A blood culture showed Friedländer's bacillus Type B, which was also demonstrated on spinal-fluid culture 2 days later. A definite diagnosis of meningitis was made and penicillin in doses of 20,000 units was given intramuscularly every 3 hours, as well as two intrathecal injections of penicillin, each containing 15,000 units. The patient received continued intramuscular and intrathecal penicillin, supplemented by 1 gm. of sulfadiazine every 4 hours, through August 26. By that time he had become increasingly ill and markedly confused and disoriented and had developed paralytic ileus.

A spinal-fluid culture on August 24 eventually showed no growth. While the results of the culture were being awaited, however, the patient's condition became progressively worse, and it was believed that he could not possibly survive unless some heroic measures were instituted.

On the night of August 26 a dose of 0.05 gm. of streptomycin was injected intracisternally at 10:00. At midnight 1.0 gm. of streptomycin in 1000 cc. of physiologic saline solution was given intravenously, and the same dose was repeated every 8 hours. Intracisternal injections of 0.05 gm. of streptomycin were again given on August 27 and August 28. The spinal fluid, which on August 25 had become gelatinous to the point where only drops could be obtained even by suction, became less viscid. His condition seemed to be unchanged until the morning of August 29, when the patient's color suddenly became poor, the pulse more rapid and the respiration somewhat labored. Approximately 2 hours later he suddenly became pulseless and slightly cyanotic and within a few minutes stopped breathing. He was pronounced dead at 11:15 a.m.

Autopsy. At post-mortem examination, performed on August 29, the significant findings were confined to the lungs and brain. The immediate cause of death was represented by small coiled emboli in the branches of both pulmonary arteries. Although the source of these clots was not identified, it was assumed that they came from the small veins of the leg. The apex of the right lung was occupied by an extensive old dense scar. In the upper part of the right lower lobe there was a group of small abscess cavities averaging about 1 cm. in diameter and having ragged walls and purulent contents. Adjacent to these cavities the parenchyma of the lung had a tough, grayish-yellow appearance, suggesting an organized pneumonia. The left lung was essentially normal, except for the emboli and some emphysematous blebs.

Microscopically, the right apex showed old dense collagenous tissue, with anthracotic pigment and a few surviving alveoli lined by cuboidal cells and containing phagocytes with foamy cytoplasm. There was also much peribronchial fibrosis, with scattered lymphocytes. The walls of the abscesses were fairly dense and fibrous, the exudate within them showing striking evidence of healing, with a predominance of large macrophages having a finely vacuolated cytoplasm (Fig. 1). There were also a few lymphocytes, plasma cells

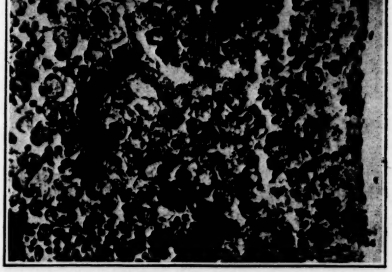

FIGURE 1. *Photomicrograph of Wall of Pulmonary Abscess (phosphotungstic acid-hematoxylin — x 400).*

The exudate is composed largely of phagocytes, with foamy cytoplasm, and a few lymphocytes and polymorphonuclear leukocytes.

and polymorphonuclear leukocytes. Careful examination of sections stained by Giemsa's method revealed no bacteria. In the area of the abscesses there was an organizing pneumonia with a similar type of exudate.

The operative wound in the brain appeared clean, and the leptomeninges of both brain and spinal cord were grossly thin and delicate. Microscopically, however, there was the picture of a healing meningitis. The meninges showed an apparently edematous fibrillar connective tissue, scattered through which there were relatively scarce cells, most of which ap-

peared to be large mononuclear cells or monocytes, many of them having indented nuclei and pink-staining cytoplasm without definite evidence of phagocytosis (Fig. 2); there

FIGURE 2. *Photomicrograph of Meninges (hematoxylin and eosin — x 400).*
Note the scattered mononuclear cells.

were also a few lymphocytes. There was no acute polymorphonuclear reaction, and no bacteria were seen in the Giemsa-stained sections. The brain tissue appeared normal. Sections of the dura showed an organizing blood clot with a few polymorphonuclear leukocytes but no bacteria. There was some amorphous bluish-staining material suggesting fibrin foam. Unfortunately, the results of culture were not available.

The anatomical diagnoses were as follows: wound of recent operation (craniotomy for removal of meningioma); healing meningitis; pulmonary apical scars; healing pulmonary abscesses and resolving pneumonia (right lower lobe); pulmonary emboli (bilateral); and hydrothorax (bilateral).

DISCUSSION

On August 21 and again on August 23, Friedländer bacilli were cultured from the spinal fluid in this case. In spite of the fact that spinal-fluid culture on August 24 showed no organisms, the facts remain that the spinal fluid became increasingly gelatinous subsequent to that day and that the patient's clinical progress was increasingly unsatisfactory. It is significant that after the administration of streptomycin the spinal fluid became less viscid and that at autopsy careful study of the meninges and of the surface of the brain disclosed evidence of a nearly healed meningitis. Whether such a finding might have presented itself with the continued use of penicillin alone is a question that cannot be answered. The complete disappearance of the extreme viscosity of the spinal fluid is regarded as having been due to the effect of streptomycin. It must be conceded that the absence of gelatinous accumulation and of any viscid accumulation was a surprising and dramatic finding. It may fairly be stated that this man did not die of a Friedländer-bacillus meningitis. His death was due to pulmonary embolism incident to a thrombophlebitis occurring in his lower extremities during the course of his illness.

SUMMARY

A case of Friedländer-bacillus meningitis treated with streptomycin administered intravenously and intrathecally is presented. The spinal-fluid changes during treatment and the complete absence of gross and the nearly complete absence of microscopical evidence of meningitis at autopsy are stressed.

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Correction. Several errors appear in the paper "Clinical Malnutrition in Italy in 1945" by Drs. Metcoff and McQueeney, which appeared in the September 26 issue of the *Journal.* In Table 2, under the heading "Anemia," both the third and fourth percentage figures should be changed from "4.3" and "5.7" respectively to "1.6," and in the second footnote, the number of cases should be changed from "70" to "258." In Table 3, under the same heading, the sixth percentage figure should be changed from "6.4" to "18.8," and in the second footnote, the second sentence should read, "Determinations made in 942 cases of the total population."

MEDICAL PROGRESS

OTOLARYNGOLOGY

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THE following summarized articles, which appeared in the literature on otolaryngology during 1945, were selected as being of general interest.

THE EAR

Fenestration Operation

Fenestration of the labyrinth for the purpose of providing better hearing in otosclerosis is now a well established and widely performed operative procedure. Although many advances have been made in the technic of operation and the proper selection of patients, closure of the fistula by the formation of new bone remains the current postoperative bugbear.

With the latest modification in his technic, Lempert[1] believes that he has solved the two major causes of previous failure: osteogenic closure of the newly created vestibular fenestra and damage to the organ of Corti by postoperative serous labyrinthitis. The modification consists of placing a cartilage stopple in the fenestra; the cartilage, which is obtained from the spina helicis, is regarded as ideal for the purpose, since it is smooth, inert and nonirritating to the endolymph and yet hard and tough enough to block osteogenesis in the bony rim of the freshly cut window and sufficiently light and elastic to transmit sound impulses efficiently. Fifty patients selected because of satisfactory evidence of good cochlear-nerve function were operated on, so that operative success and failure alike could, with fairness, be traced solely to the operation itself. The results were reported as 100 per cent successful. Partial or total closure of the fenestra had occurred in 140 of the 1000 patients operated on by Lempert during the previous seven years. Eighty-eight of these closures took place in the first 300 cases, in which fenestration was done in the prominence of the external semicircular canal. In the last 700 cases, in which the fenestra was made in the surgical dome of the vestibule, fifty-two closures occurred.

Day[2] reports that the operation is extremely difficult and tedious, usually requiring two and a half to three and a half hours. Moreover, the procedure is not bloodless, painless or devoid of danger. Since it is a purely mechanical method to create a new pathway for the transmission of sound waves to the cochlear end organ, it does nothing toward removing or eliminating the otosclerotic foci and does not restore lost nerve function. Despite many failures, however, brilliant results have been achieved in restoring practical conversational hearing to an increasingly large number of persons with otosclerotic deafness. An analysis of the results of the operation in cases submitted to the Otosclerosis Study Group reveals that in 211 cases in which the original operation, which involved the horizontal semicircular canal, was performed, improved hearing followed in only 47 per cent, and hearing reached a satisfactory level of understanding of normal speech in only 10 per cent. With the revised operation, in which the window is created in the roof of the vestibule, 76 per cent of 554 patients had improved hearing, but in only 31 per cent did the hearing reach the practical level. The only justifiable purpose for the operation is to restore practical conversational hearing, and cases reported as successful should be limited to those in which the hearing reaches this level. The practical level of hearing for normal conversation is somewhere around the level of 25 decibels. Therefore, if a patient has a loss of 70 decibels and the operation gives him a 30-decibel improvement, he is still unable to understand normal speech and the operation should not be considered successful. Not more than 10 per cent of patients with otosclerosis are considered suitable for the operation, which should be reserved mainly for adolescents and young adults. Patients over forty years of age usually have secondary nerve degeneration that prevents their hearing from reaching a practical level after operation. Good bone conduction is regarded as essential, since hearing loss by bone conduction indicates nerve damage and cannot be restored by operation. A hearing aid is preferable to operation in cases in which a high postoperative hearing level cannot reasonably be expected to result. In Day's series of 75 cases, a good result with practical hearing for conversation was obtained in 40, or 74 per cent, of 54 patients operated on between October, 1941, and June, 1944. In 3 cases the fenestra closed but was successfully reopened, making a total of 43, or 80 per cent, with successful results. Average hearing loss for the speech range for pure tones before operation was 48.2 decibels. Following operation, there was an average improvement of 28.5 decibels and an average hearing loss in the speech range of 19.7 decibels.

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The conclusion was reached by Berry[3] that a well fitted hearing aid could give greater sound amplification and furnish help to a wider group of patients at the cost of less pain and worry than could a fenestration operation. On the premise that hearing for speech is more important than hearing for pure tones, as measured by standard audiometers, Shambaugh[4] retested Berry's conclusions and surveyed a group of patients on whom the fenestration operation had been performed after the use of hearing aids, to get their impression of the comparative benefits. The testimony was predominantly in favor of the operative result. According to Shambaugh, the hearing aid shows to best advantage under standard test conditions — that is, in a soundproof room in which there is little interference of static, distortion and amplification of outside noises, all of which combine to hamper the hearing for speech. So that subjective impressions might be ruled out, 14 patients, each of whom had worn a hearing aid before operation and had been tested by means of a speech audiometer, with and without the aid, both before and after fenestration operation, served as the basis for the following conclusion: patients with an average gain (20 decibels or more with the pure-tone audiometer) in hearing after the fenestration operation had better hearing for speech than they had with hearing aids before operation, and those who obtained less than the average gain in hearing for pure tones were not benefited. On the basis of one-year results with the fenestration operation as it is now used, the further conclusion is reached that the ideal subject for the fenestration procedure has about a 90 per cent chance of securing permanently better hearing and a 70 per cent chance that the hearing will be as good as, or better than, it was with a hearing aid.

Congenital Deaf-Mutism

Carruthers[5] reports that in Australia, especially during the years 1940, 1941 and 1942, an exanthematous disease, believed to be rubella, occurred in widely scattered parts of the country. There was a greater tendency than usual for adults, and especially young adults, to contract the disease. A proportion of pregnant women had this disease, which, although minor for the mother, had disastrous effects on the developing fetus, as revealed at birth. Congenital cataracts, cardiac defects and anomalies, deaf-mutism, microcephaly, general stunting of the growth and dental defects were reported. The stage of pregnancy at which the infection occurred was apparently most important in influencing the type and extent of congenital defects. If infection occurred during the first six weeks, fetal damage was widespread, including the eyes, both divisions of the ears, the heart and perhaps many other organs. After the sixth week the eyes sometimes escaped, the heart was spared and the semicircular canals developed normally, but the cochlea was still likely to be damaged and growth was sometimes retarded. After the third month damage to the fetus was rare. Apparently there was no correlation between the severity of the infection in the mother and the degree of fetal damage. Since deafness is often not discovered until it is evident that speech development is retarded, it is not yet possible to state exactly what proportion of children born of mothers who had rubella during pregnancy have severe hearing defects, although it is likely that the figure is over 50 per cent. Of 102 children with congenital defects whose mothers were known to have had rubella during pregnancy, 74 were deaf and 14 of these also had congenital heart lesions. The most frequent type of congenital anomaly in deaf-mutism is that in which the middle ear and the bony form of the inner ear are normal and the vestibule and semicircular canals are more or less normal in development but in which the cochlea, especially Corti's organ, and the saccule show evidence of maldevelopment. Congenitally deaf-mute infants whose deficiency is the result of maternal rubella belong to this group, for these patients are quite deaf but not completely insensitive to sound and, so far as they have been tested, give evidence of an active, although reduced, vestibular apparatus. Many children gave evidence of loss of hearing over the tone range 512 to 2048. Tests of caloric labyrinthine reactions in 9 cases showed slightly reduced responses as compared to normal. An interesting feature of the test was absence of sickness from caloric stimulation, even when a pronounced nystagmus was induced. By contrast with the gross inactivity of the cochlea, it is obvious that often the semicircular canals were largely spared. In the series of Carruthers 17 deaf-mute children were under observation, the oldest of whom was six and a half and the youngest three and a half years. At the age of three and a half years several children began to use their hearing. It is hardly possible that the receptive function of the inner ear actually developed; rather, it is believed that the children began to take some interest in their residual powers as a result of mental growth and training. Parents are instructed to use every means to preserve the baby voice until such a time as special training is practicable.

Pregnancy and Otosclerosis

Allen,[6] in a review of the literature regarding the possible etiology of otosclerosis, discussed the effects of pregnancy on deafness, as observed in 18 cases without audiograms, including 13 by personal communication and 5 from the literature, and 54 cases with audiograms, including 19 by personal communication and 35 from the literature. No change in hearing occurred in 24 cases without and in 8 with audiograms. The otologists believed that decrease in hearing was consistent with that which

might be expected during the normal progress of the disease. Hearing was decreased beyond normal expectancy in 30 cases without audiograms and in 5 with audiograms. In 4 cases deafness first occurred during pregnancy. For progressive deafness to be considered an indication for therapeutic abortion, a definite diagnosis of otosclerosis must first be made. The hearing should be followed carefully before, during and following pregnancy and lactation for evaluation concerning succeeding pregnancies. Otosclerosis should not be considered as an indication for therapeutic abortion in primiparas. A familial history of deafness need not be present and yet may be one of the deciding factors in the decision to interrupt a pregnancy. A multipara may have considerable right to question the continuation of her pregnancy, if accurate otologic evidence obtained at previous pregnancies has shown a marked, sustained loss of hearing. Before therapeutic abortion is decided on, the patient should be informed that otosclerosis is a progressive disease, even without pregnancy, and that hearing aids and lip reading offer considerable help.

Barton[7] made a study of the effect of pregnancy on the hearing of 133 women who were known to have otosclerosis and who had one or more pregnancies. In 73 patients the hearing was made worse by pregnancy, and in 51 of these the hearing loss occurred during the first pregnancy and persisted in all but 2 of the patients. In multiparas who experienced loss of hearing with the first pregnancy, about 50 per cent showed no further loss with subsequent pregnancies. It was concluded that therapeutic abortion or sterilization is not indicated in women with otosclerosis, since the hereditary nature of the disease has not been conclusively proved and the unfavorable effect of pregnancy on the hearing is not constant.

Penicillin in Otology

Johnson and his associates[8] report a series of 23 cases in which a simple mastoidectomy was performed for suppurative mastoiditis following scarlet fever or measles. The mastoid wound was sutured, penicillin being applied to the cavity through a urethral catheter. The recommended dose of the drug was 10,000 units every eight hours for four days. Seventeen patients showed a complete cure after one course of treatment, whereas 6 remained well after a second course. When penicillin was given in adequate dosage, healing of the postaural wound and a dry external auditory canal usually occurred on the fifth postoperative day. If aural discharge recurred, the catheter was reinserted and more penicillin was injected until the ear had completely cleared. Local treatment with penicillin seems preferable to the use of sulfonamides when susceptible organisms are present, because of the absence of any harmful toxic effects, the slight risk of sensitization and the increased speed of healing.

Allman[9] used penicillin intramuscularly in 511 cases of otitis media caused by scarlet fever. Twenty-seven cases of scarlet-fever mastoiditis were cured in this manner without surgery. In 33 cases of mastoiditis due to scarlet fever, penicillin was used both intramuscularly and locally; these cases required surgical exenteration of the mastoid. Meningitis occurred in 2 patients. In the postoperative treatment of 14 cases of non-scarlet-fever mastoiditis, penicillin was administered by the same method. Ten of these patients had acute and 4 had chronic mastoiditis. Administration of the drug by the intramuscular route was accomplished by giving 20,000 units at the onset and following this by 10,000 units every three hours thereafter day and night until the tympanic membrane and the postaural incision were healed. For local application within the mastoid cavity, 10 cc. of a solution containing 500 units of penicillin per cubic centimeter was instilled into the mastoid cavity every four hours when the cavity was large, and 5 cc. when it was small. Sodium penicillin was used. The postaural incisions healed by primary intention. Administration of penicillin from the onset of scarlet fever reduces the incidence of ear complications. In a study of 300 patients with scarlet fever in the wards in which no penicillin was administered, acute otitis media developed in 10.9 per cent, whereas in wards in which penicillin was administered, the incidence in 300 cases of scarlet fever was only 5.6 per cent.

Otitis Externa

Senturia's[10] studies on external otitis at Randolph Field, Texas, show that fungi play little part in the inception or persistence of external otitis. Gram-negative bacilli, especially those of the Pseudomonas group, were found in a high percentage of cases showing acute desquamative and chronic suppurative external otitis, but no single organism or combination of bacteria occurred frequently enough to be considered a specific cause of external otitis. Bacterial infection produces almost any type of discharge, from a thin serous type to a thick, grayish, purulent secretion. The so-called "blotting-paper" discharge is not pathognomonic of fungus infection. It was concluded that, since no single available chemotherapeutic agent is an effective bactericide and fungicide for use in acute infections of the ear canal, careful examination and observation of all types of external otitis are necessary.

In a series of 90 cases of otitis externa in a tropical climate studied by Simon,[11] only 20 per cent showed cultures yielding a fungus. The presence of an organism in culture from otitis externa does not absolutely imply that the organism is the primary agent; it may or may not be the one producing the lesion. In each of the 90 cases, a bacterial growth on culture was obtained, and it was concluded that bacteria are the primary invaders in this disease. In the last 60 cases the external auditory canal and

drum were thoroughly cleaned and dried and the canal wall and drum membrane were sprayed with a coating of sulfanilamide. Every four hours 1 gm. of sulfathiazole was administered, and if no improvement was noticed, the dose was increased to 1.5 gm. every four hours. If sulfathiazole was not tolerated, sulfadiazine was used. This routine, which was continued until the discharge, edema and itching subsided, was successful. The average duration of treatment in this series in a tropical climate was less than seven days.

Radium Therapy for Aerotitis

Irradiation of the nasopharynx by radium for the control of aerotitis proved to be safe and effective prophylaxis and treatment as used by the United States Army Air Forces.[12] The flying personnel treated numbered 6881, but owing to the shifting of personnel only 1129 men were available for observation thirty days or more after the completion of the therapy. The conclusions reached are based on the study of this group. Seventy-four per cent of 636 men with a history of recurrent aerotitis had less difficulty in ventilating their ears during flights. Eighty-nine per cent of the same group showed a marked decrease in the amount of nasopharyngeal lymphoid tissue when examined with a nasopharyngoscope thirty days or more after the third treatment. The beneficial effect of prophylactic irradiation was shown by the drop in incidence of aerotitis in 778 men after high-altitude flights. Following the completion of treatment, the incidence of aerotitis in this group was reduced from twice that in a control group of 922 men with normal nasopharynges to a level almost identical with that in the control group. The principal cause of failure to improve after irradiation treatment was the presence of a large mass of adenoid tissue. For such patients, surgical removal, supplemented by irradiation, would have been more effective. Other contributing factors to failure of treatment were considered to be nasal allergy, chronic sinusitis and psychologic reactions. Treatment consisted in placing two nasopharyngeal applicators, each containing 50 mg. of radium sulfate, in the nasopharynx for a period of eight and a half minutes. From one to three treatments were given at intervals of eight days. In 14,045 treatments there was not a single case of burn or ulceration of the nasopharynx or nasal mucous membrane.

Surgery of Facial Nerve

Tickle[13] reports his observations on 300 operations for peripheral facial paralysis performed since 1930. When interruption of the continuity of the nerve was due to trauma, fresh nerve grafts from the anterior femoral cutaneous nerve were used to bridge the gap. Grafts from either motor or sensory nerves may be employed, but the latter are regarded as preferable. Two types of nerve injury respond to surgery: trauma to the facial nerve and Bell's palsy. Patients with facial paralysis following trauma should be tested daily with the faradic current. So long as any response occurs, operation should be deferred, but if reaction to the faradic current is lost, the nerve should be investigated immediately. In Bell's palsy, 85 to 90 per cent of patients recover; the remainder can be helped by decompression of the nerve if this is done soon after the onset. As in trauma, the same criteria apply for determining the time to operate. Patients who retain response to the faradic current recover; those who lose this response may never, or only partially, recover. If response to galvanic stimulation is lost in either type of case, operation is useless, for this means atrophy or fibrosis of the facial musculature.

Nose and Sinuses

Chemotherapy

Kern[14] condemns the use of sulfonamides in the common cold because of the risk of inducing sensitivity to a drug that may later be required in a more serious infection. Furthermore, the doses employed are usually inadequate to prevent pneumonia, and yet this inadequate dosage can be responsible for a drug-fast strain of the pneumococcus. Administration of these drugs renders the pneumococcus untypable and thereby prevents the use of specific serum therapy in patients with drug-fast pneumococci. Routine administration of the sulfonamides, which may interfere with the development and maintenance of a desirable active immunity to a number of frequent pathogenic organisms, may increase the incidence of pyogenic complications in the respiratory tract in the period immediately following the cold.

Hayden and Bigger[15] gave sulfanilamide lozenges, each containing 0.065 gm. of the drug, to a group of troops in an Army training center. A similar group were given lozenges of the same base but lacking the sulfanilamide. The lozenges were administered five times daily for sixteen days. From the observations on these groups, it was concluded that if the sulfanilamide lozenges afforded any protection against colds, it was of such an insignificant degree as to be not worth the trouble, expense and risk involved.

In the treatment of acute sinusitis and its complications, Hauser and Work[16] favor the intramuscular injection of 20,000 units of penicillin every three hours until the optimum result has been obtained. In the treatment of orbital cellulitis, this therapy has replaced every other method of treatment. In the presence of allergic rhinitis with superimposed infection, penicillin therapy eliminates all evidence of suppuration but produces no change in the underlying allergy. The results obtained in chronic sinusitis depend to a large extent on the duration of the disease. When the duration is relatively short, a cure can be accomplished by the in-

tramuscular injection of penicillin alone. In chronic suppurative disease of the sinuses of long duration, penicillin alone is of little value, but when used in conjunction with adequate sinus surgery, rapid and complete cures were accomplished.

Sinus Disease in Children

According to Taquino,[17] two facts are generally overlooked in sinus disease in children: that it is frequent and that it is often of allergic origin. Diagnosis presents some difficulty because of the age of the patient and the size of the nasal passages. Transillumination of the sinuses is regarded as unreliable, and even radiologic information may be misleading. The same diagnostic procedures that are employed in adults should, however, be carried out in children for the diagnosis of sinus disease. In general, treatment should be of a conservative nature. Removal of the tonsils and adenoids should not be done unless definitely indicated. The routine use of chemotherapy is undesirable. The type of organism found in the sinuses should indicate the chemotherapeutic agent to be employed. Whenever drainage of the sinuses is necessary, it should be carried out by the simplest method. Sinus disease of allergic origin must be treated primarily as an allergy. In both types of sinus disease, attention to the general health is of the greatest importance.

Frontal-Sinus Surgery

In a series of 123 cases in which the Lynch operation for chronic infection of the frontal and ethmoidal sinuses had been performed, Goodale[18] reports that reoperation was necessary in approximately 30 per cent. At the second operation, the causes for failure were noted as follows: obstruction of the nasal frontal passage by adhesions; remnants of the frontal-sinus floor that had given rise to undrained infected pockets in the frontal sinus; and incomplete ethmoidectomy, especially failure to remove orbital extensions of the ethmoid. To maintain the patency of the opening between the frontal sinus and the nasal cavity, a strip of tantalum foil, 1.5 cm. wide and 4.0 cm. long, was sutured by means of fine tantalum wire to the orbital periosteum, at about the position of the pulley. During the previous two years, this technic had been used with excellent results in a total of 8 patients.

Pharynx and Tonsils

Monilial Pharyngitis

Tumulty and Michael[19] report a series of 18 patients with monilia infection of the oropharynx. Although the disease usually occurs in undernourished infants or debilitated adults, the patients reported were well nourished young men in good general health. There is no clinical feature of monilial pharyngitis that helps to differentiate it from streptococcal pharyngitis or from pharyngeal diphtheria. Secondary syphilis and Vincent's angina may also cause some confusion. The diagnosis is made by direct examination of mucosal scrapings and by culture material obtained from diseased sites. Throat swabs should be planted on slants of Loeffler's medium. If monilia are present, small creamy colonies appear after twelve to eighteen hours of incubation. Overnight growths are stained with Loeffler's methylene blue, and either monilia or diphtheria organisms can be demonstrated by this method. In 5 of the cases reported, monilia was considered solely responsible for the acute pharyngitis. In 3 other cases, its significance could not be determined owing to the presence of beta-hemolytic streptococci. In the remaining cases, it was believed to have had no etiologic role.

Poliomyelitis and Recent Tonsillectomy

Anderson[20] reports that a severe epidemic of poliomyelitis occurred in Utah in 1943. Of the hospitalized patients, 31.6 per cent had the bulbar or bulbospinal type. A state-wide survey showed the number of tonsillectomies performed to be 1411 in July, 2111 in August and 677 in September. Seventeen of these children developed poliomyelitis within thirty days after operation; all the patients had either the bulbar or bulbospinal type of poliomyelitis. During the same three-month period, 261 cases of poliomyelitis were reported in the state, in which 232 patients were children between the ages of three and sixteen. The incidence of poliomyelitis in the tonsillectomized group was 0.40 per cent, or about two and a half times greater than the 0.15 per cent incidence of poliomyelitis in the child population of the same age group. The total number of bulbar or bulbospinal cases of poliomyelitis in children three to sixteen years of age was 39; and 17 (46 per cent) of these cases had been preceded by a recent tonsillectomy. A comparison of the incidence of bulbar cases in the general child population with the incidence in the tonsillectomized group showed that, during this epidemic, the possibility of contracting bulbar poliomyelitis was sixteen times greater in children immediately after tonsillectomy than in children in the general population.

Post-Tonsillectomy Hemorrhage

According to Singer,[21] post-tonsillectomy hemorrhage occurs in 5 to 10 per cent of all tonsillectomized patients. In the clinics and hospitals of Central Europe, the incidence of this complication is practically nil because of the practice of giving aminopyrine instead of acetylsalicylic acid. A comparison of the preoperative and postoperative regimes used in this country and abroad show this to be the only significant difference. In 75 patients observed during 1943 who, after tonsillectomy, were placed on an acetylsalicylic acid-free post-tonsillectomy routine, no secondary hemorrhage occurred and, what is regarded as more significant, no case of

hemorrhagic inflammation of the soft palate was observed.

Neivert[22] reports that, with rare exceptions, observations to date suggest that one of the most important factors in late post-tonsillectomy hemorrhage is the reduction of the prothrombin of the blood brought about by the use of acetylsalicylic acid or salicylates. This reduction in prothrombin interferes with coagulation. With the simultaneous administration of Synkavite, a compound similar to vitamin K, the prothrombin-lowering effect of acetylsalicylic acid is overcome and normal coagulation can take place. Rectal suppositories and tablets composed of 0.3 gm. of acetylsalicylic acid and 5 mg. of Synkavite were used. Suppositories were given to 173 patients, and the tablets to 110 patients. The results were reported as most gratifying, late tonsillar bleeding occurring in only 4 patients among the total of 283 — an incidence of 1.4 per cent. When compared with an incidence of late tonsillar hemorrhage of almost 10 per cent accompanying the former routine, which called for the free use of salicylates alone, the present results demonstrate that proper postoperative care should include measures designed to prevent lowering of the prothrombin content of the blood. It is concluded that salicylates should either be avoided or, if given, combined with a drug such as Synkavite, which prevents hypoprothrombinemia.

Sulfathiazole in Chewing Gum

In treating a series of patients who had infections of the mouth, tonsils or pharynx, Fox and his associates[23] used a tablet of gum containing 0.25 gm. of sulfathiazole. One tablet was administered every three hours, except when a severe infection of the throat was present, when the patient was instructed to chew the tablet for an hour and to rest for an hour. In 52 cases of acute lymphoid pharyngitis and follicular tonsillitis, 72 per cent showed a decided decrease in total bacterial counts of cultures made from mouth washings within forty-eight hours, along with complete disappearance of the beta-hemolytic streptococcus from the cultures. In 38 cases of ulcerative stomatitis, a decrease in the total bacterial count was noted in 67 per cent, with a 75 per cent decrease in the beta-hemolytic streptococcus within forty-eight hours. Even more spectacular was the rapid clinical resolution of these conditions. The same results were obtained in the Plaut–Vincent ulcerative type of stomatitis. In chronic mouth conditions, such as salivary adenitis and catarrhal stomatitis, associated with mouth breathing in persons with hyperplastic pansinusitis, a decrease in the total bacterial count was also noticed. Clinical improvement, as demonstrated by the disappearance of mouth odor and coated tongue, was observed. It was concluded in this preliminary report that, from the standpoint of minimal systemic toxicity and maximum local antibacterial potency, sulfathiazole in chewing gum is the preferable local chemotherapy for infections of oral and pharyngeal mucosa that are susceptible to the sulfonamides. The best clinical results were obtained in conditions of the mouth and pharynx in which the beta-hemolytic streptococcus was the predominant organism.

Larynx

Hoarseness

Zinn[24] points out that hoarseness may result from inflammatory infections of the larynx, trauma, tumors and disturbances of the central and peripheral nervous systems. The diagnosis of functional hoarseness should not be made until all organic lesions have been excluded. This condition requires as careful study and treatment as if a definite lesion were present. It is now generally conceded that 80 per cent of all cases of carcinoma of the larynx are curable by operation if the diagnosis is made while the disease is still intrinsic. In a previously reported series of 25 cases of total laryngectomy, 80 per cent of the patients gave a history of preoperative hoarseness for periods varying from six months to over two years. In another series of 178 cases, hoarseness was a constant symptom, but 100 of the patients, who were not referred until all classic symptoms of carcinoma were present, had to be classed as inoperable. Of 144 cases of carcinoma of the larynx recently examined, 134 patients (93 per cent) gave a history of hoarseness as the first symptom. Jackson and Jackson[25] report statistics on 410 cases, in which hoarseness was an early symptom in 95 per cent. Negus[26] urges that no patient be continuously hoarse for more than three weeks without laryngeal examination and diagnosis.

Cancer of the Larynx

According to Tucker,[27] in a large number of cases surgical cure of cancer of the larynx by laryngofissure and total laryngectomy has been reported, and it is his belief that surgery is the method of choice in the treatment of this condition, when adequate excision can be performed. Surgical excision by laryngofissure should give a permanent cure in from 80 to 85 per cent of cases in early intrinsic cancer. In more extensive lesions in areas of the larynx where metastatic extension is more rapid, total laryngectomy is required, and a cure of from 50 to 60 per cent of advanced cases of this type may be expected. When the lesion has extended beyond the cartilaginous framework of the larynx, wide excision of the involved area with removal of the larynx, followed by postoperative irradiation, offers a fair prognosis — possibly 30 to 50 per cent of the patients are cured. The possibility of late recurrence of cancer in the regional lymph nodes, without local recurrence in the larynx, following laryngofissure or local recurrence in the pharynx or trachea following laryngectomy must be kept in

mind, for metastatic lymph nodes have appeared from five to ten years after surgical excision of the primary lesion. The mass should be removed immediately by surgery, radon seeds implanted in the region from which the node was removed and x-ray irradiation applied to the neck. Jackson and Norris[28] use the following indications for surgical treatment of cancer of the larynx: lesions occupying the middle third of one cord are suitable for laryngofissure; lesions reaching the anterior commissure and even involving the opposite cord are also amenable to extirpation by the laryngofissure route, but in such cases the so-called "anterior-commissure" technic should be used; lesions in which the growth is cordal but has reached the posterior end of the cord and produced impairment of motility or has extended subglottically ordinarily call for total laryngectomy, as do lesions involving the ventricle or ventricular band; and lesions in which the tumor has invaded cartilage (but not muscle) also call for laryngectomy, provided there are no metastases — where there are metastases, combined laryngectomy and neck dissection should be done. Irradiation is regarded as preferable in lesions unsuitable for laryngofissure in which laryngectomy is contraindicated by the age, physical condition or temperament of the patient, and also for growths inoperable because of extrinsic origin or extension or because of cervical metastases. An analysis of the end results in a series of 150 patients with cancer of the larynx treated at the Temple University Hospital by surgery and irradiation from 1930 to 1937 inclusive showed a combined five-year cure rate of 64 per cent. Of 101 patients with intrinsic lesions who received surgical treatment by either laryngofissure or laryngectomy 80 patients, or about 75 per cent, obtained at least a five-year cure. Nine patients with extrinsic lesions, on whom laryngectomy was performed, died. During the same period, 34 patients were treated by irradiation (protracted fractional technic), 22 with intrinsic and 12 with extrinsic growths; in the former group, a 59 per cent and in the latter a 25 per cent five-year cure rate was obtained.

Hemangioma of the Larynx

Kasabach and Donlan[29] state that the possibility of hemangioma should be considered in infants when there is a history of recurring, obstructive dyspnea. The symptoms of hemangioma of the larynx in infants, in order of frequency, are obstructive dyspnea, inspiratory stridor, a hoarse cry, croupy cough, blood-tinged mucus, gross hemorrhage and fever, if there are pulmonary complications. Laryngoscopic examination shows a red or bluish subglottic mass. The presence of other hemangiomas on the body also helps to confirm the diagnosis. Hemangiomas of the larynx in infants are always subglottic, whereas in adults they are usually found on or above the vocal cords. In the treatment of hemangioma of the larynx in infants, the dyspnea must first be relieved by low tracheotomy; radiation therapy is then begun, using either radium or x-ray. Two cases were reported in which x-ray therapy was used with good results; both children were normally developed and had adequate airways two years or more after the completion of treatment.

Recurrent-Nerve Paralysis

Laszlo and Fiertz[30] have been successful in determining the prognosis in cases of recurrent-nerve paralysis following thyroidectomy. The principle of examination follows the same underlying criteria as the electrodiagnosis of any other peripheral-nerve injury. The necessary equipment consists of an electrical apparatus that provides both a straight galvanic and a faradic current. A flat electrode is placed on the sternum and the nerve-testing electrode is put on the motor point for the vocal cord — that is, on the respective side of the Adam's apple. If a faradic response is obtained, the damage is minor and recovery can be expected in about two months. If, in the absence of any faradic response, the cathodal closing contraction is better than the anodal response, the second stage of the reaction of degeneration is present and recovery cannot be expected within less than nine months. If the formula is reversed, a complete reaction of degeneration is present and the outlook is accordingly worse. Whether or not the nerve has been anatomically severed cannot be determined by one examination alone, but if, after two months of biologically correct treatment, re-examination gives the same or a worse formula, the conclusion is that the nerve is cut and further conservative therapy is useless. If, however, the formula or the quality of the contraction has improved, treatment can be continued, although the time for recovery may require one and a half or two years. If no reaction whatever is obtained, the diagnosis is obvious and no benefit may be expected from electrotherapy.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 32451

PRESENTATION OF CASE

First admission. A seventy-four-year-old man entered the hospital because of gross urinary bleeding of two weeks' duration. The bleeding was painless and there were no other symptoms. On examination, the left lobe of the prostate was slightly enlarged and firm; the left testicle was atrophied, and there was a reducible left inguinal hernia. Cystoscopy revealed a small, sessile growth with superficial papillary projections located deep in the left ureteral orifice. Treatment consisted in cutting away the tumor in pieces and implanting four radon seeds of 1 millicurie each. The pathological report was carcinoma (Grade III). The patient was discharged on the eleventh day.

Final admission (four years and six months later). During the period following operation, the patient visited the Out Patient Department every six months. The bladder wound healed, leaving a white scar. No recurrence was apparent at any time. The lateral lobes of the prostate became slightly enlarged and more indurated. There was slight inflammatory edema of the bladder outlet. Two years before admission the patient began to be constipated. Approximately six months before admission he began to notice bright-red blood in the stools, continuing until admission; the stools were never black. About a month later he noticed a small painless lump in the right neck that had progressed to 3 cm. in diameter by the time of entry. The patient believed that he had begun to lose ground about a month before admission. His appetite failed, and he lost all sensation of taste. He had lost 15 pounds in weight during the preceding year. The throat became dry and somewhat sore. A diffuse, dull, crampy epigastric pain unrelated to food and slightly relieved by soda annoyed him constantly. Blood was said to have appeared in the urine at about the same time. Three weeks before admission the skin turned yellow, and the jaundice subsequently deepened. The stools became light colored in the weeks before entry.

On physical examination the patient was thin and jaundiced and spoke with a hoarse voice. On the right side of the neck beneath the sternomastoid muscle was a mass, 3 by 4 cm. in diameter, that was hard and only slightly movable. The chest was clear. The liver extended 4 cm. below the ribs. There was a right indirect hernia, and the right testicle was atrophic. The right lateral lobe of the prostate was firm, with a poorly defined border.

The temperature was 98°F., the pulse 65, and the respirations 15. The blood pressure was 120 systolic, 60 diastolic.

Examination of the blood showed a hemoglobin of 12 gm. per 100 cc. and a white-cell count of 6050. The urine was bile stained, gave a ++ test for albumin and contained rare white cells per high-power field but no red cells. The stools were fluid, brown and grossly bloody. X-ray films failed to reveal metastases in the chest. No definite esophageal lesion was seen, but there was delay in the passage of barium through the lowermost portion of the esophagus where it crossed the aorta. The duodenal bulb was deformed in a manner characteristic of an old ulcer. The only abnormal blood values were a bilirubin of 17 mg. per 100 cc. direct and 20 mg. indirect, a prothrombin time of twice normal and a chloride of 97 milliequiv. per liter. The cephalin-flocculation test was + in twenty-four hours and ++ in forty-eight hours. The acid phosphatase level was 1 unit, and the alkaline phosphatase 16.3 Bodansky units per 100 cc.

On the day after admission generalized itching of the skin developed. In the next two weeks three diagnostic procedures were performed. Proctoscopy disclosed an obstructing tumor in the rectosigmoid, 14 cm. from the anus, biopsies from

which showed adenocarcinoma (Grade II). Aspiration biopsy of the mass in the neck was reported as showing "metastatic carcinoma consistent with bladder origin." Peritoneoscopy revealed a large blue-gray liver. No metastases were seen in the liver or peritoneum. Omentum adherent around the gall bladder prevented visualization of that region.

On the twelfth, thirteenth, fourteenth and fifteenth days the temperature spiked to 102 to 103°F., with a shaking chill at each daily peak. Painful effusion of the right knee developed on the fifteenth day. A watery diarrhea, with partial incontinence, was the patient's major difficulty. The jaundice persisted. In the last three days the general condition deteriorated rapidly. On the eighteenth day the patient became comatose and died a few hours later.

Differential Diagnosis

Dr. Paul Zamecnik: I am curious about the occupation of this patient in view of the fact that carcinoma of the bladder is one of the few human tumors in which there is a definite occupational etiology. In the German dye industry in the early days, when making aniline and other aromatic amines began, it was found that 30 per cent of the cases of carcinoma of the bladder occurred in dye workers.

Dr. Tracy B. Mallory: I can find no record of this man's occupation.

Dr. Zamecnik: I should also like to know whether any x-ray films of the spine and pelvis were taken.

Dr. Mallory: We have x-ray films, but the radiologist says that they are entirely negative and not worth showing.

Dr. Zamecnik: The primary assumption may be made in this case that the patient died as a result of metastatic carcinoma, and the problem is then reduced to deciding which of several possibilities may be the primary site. One may list what seem to be the likelier possibilities — carcinoma of the bladder, the rectosigmoid and the prostate — and discuss them in reverse order.

Three symptoms point to disease in the neck: hoarseness, dryness of the throat and loss of taste. Carcinoma of the larynx accounts for between 1 and 5 per cent of all carcinomas. It can explain the hoarseness and all symptoms in the cervical region, but carcinoma of the larynx usually remains localized until late and seldom metastasizes to a great distance. It does not appear to be a good possibility when most of the pathologic findings relate to the abdomen.

When one is dealing with metastatic carcinoma of the prostate, the acid phosphatase activity is generally elevated and is practically always elevated when there is metastasis to bone. This diagnosis has in its favor the fact that carcinoma of the bladder frequently results from extension of the process from the prostate; indeed, possibly 50 per cent of carcinomas of the bladder are extensions from the prostate. Carcinoma of the prostate, however, metastasizes to the bone in about 70 per cent of the cases. Of this 70 per cent, about 85 per cent are osteoblastic and should be associated with a high acid phosphatase level. Therefore, although carcinoma of the prostate is a disease that frequently extends through to the bladder, one would not expect such extracapsular prostatic disease to remain dormant. On the whole, one may rule out carcinoma of the prostate.

We should also consider carcinoma of the rectosigmoid. Thirty per cent of carcinomas of the gastrointestinal tract are rectal, and of these, two thirds are rectosigmoid. I think that it is unlikely that a metastatic carcinoma would localize in the rectosigmoid region and produce an obstruction. It is more probable that disease occurred primarily in this region. Carcinomas of the rectosigmoid metastasize freely, usually to the inferior mesenteric nodes and frequently, by extension or metastasis, to the liver, lungs and brain. I believe that carcinoma of the rectosigmoid cannot be ruled out.

The final possibility is carcinoma of the bladder. When all cases of carcinoma of the bladder are taken into account, 75 per cent of the patients fail to survive five years. Usually, however, when recurrence occurs it does so locally, and metastases are generally not widespread. Death most frequently occurs as a result of obstruction of the ureters or infection of the urine and pyelonephritis. The aspiration biopsy of the mass in the neck showed "metastatic carcinoma consistent with bladder origin," so that I assume that it was a squamous-cell carcinoma. On the other hand, an adenocarcinoma was found in the rectosigmoid, and I therefore think that it is sound to assume that there were two separate primary neoplastic processes present in this patient. One was carcinoma of the bladder, which was discovered five years previously and which was treated with radon implants. There may have been some residuum in the submucosa, later metastasizing to the cervical region and possibly extending through into the prostate. The latter situation is a rather frequent process. My second diagnosis is adenocarcinoma of the rectosigmoid, with metastases to the retroperitoneal nodes, the liver and possibly the mediastinum. The terminal event may have been due to cholangitis associated with a partially obstructive jaundice, and the effusion in the knee may have been a result of terminal septicemia.

Dr. Edward Benedict: I did the peritoneoscopy on this patient, and I thought that the findings were consistent with biliary cirrhosis. I could not see metastatic carcinoma in either the liver or the peritoneum. But, of course, peritoneoscopy is

limited; it shows only surface lesions, and a retroperitoneal carcinoma can easily be missed.

Clinical Diagnoses

Carcinoma of bladder.
Carcinoma of rectum.

Dr. Zamecnik's Diagnoses

Carcinoma of urinary bladder, with cervical metastasis and probable extension through to prostate.
Adenocarcinoma of rectosigmoid, with metastases to retroperitoneal lymph nodes, liver and possibly mediastinum.
Terminal cholangitis and septicemia.

Anatomical Diagnoses

Colloid carcinoma of gall bladder, with widespread metastases.
Epidermoid carcinoma of bladder, with cervical metastases.
Adenocarcinoma of rectum.
Adenocarcinoma of prostate.
Biliary cirrhosis of liver, slight.

Pathological Discussion

Dr. Mallory: Dr. Zamecnik listed three possibilities: carcinoma of the bladder, infiltrating adenocarcinoma of the rectum and a probable cancer of the prostate. The patient had all three. The bladder at the time of autopsy showed no evidence of recurrence, but a large lymph node in the neck from which the aspiration biopsy had been taken, when removed at autopsy, showed a poorly differentiated squamous-cell carcinoma entirely consistent with bladder origin and closely resembling a bladder tumor. We also verified the fact that he had carcinoma of the prostate, which was a well differentiated adenocarcinoma resembling in no way the tumor of the bladder, and we could be quite certain that it was a second primary tumor. The tumor of the rectum was also an adenocarcinoma, but once more was well differentiated, slightly polypoid in character, showing slight invasion of the wall, and apparently entirely localized. On the other hand, the retroperitoneal lymph nodes were diffusely and markedly enlarged and, on gross examination, obviously filled with carcinoma.

We also found at autopsy a gall bladder that had a thick, firm, hard wall and a diffuse thickening of the wall of the common bile duct. There was a large stone in the gall bladder, as there usually is in cases of primary carcinoma of the gall bladder. The gall-bladder tumor showed quite marked mucin formation, and the majority of the metastatic lymph nodes showed a frank colloid carcinoma, whereas there was no suggestion of colloid formation in the rectal tumor. Our final opinion on this case was that the patient had four independent primary cancers and that it was the cancer of the gall bladder that produced the metastases and resulted in death, and not the other three that were apparent on clinical examination.

CASE 32452

Presentation of Case

A twenty-seven-year-old crane operator entered the hospital for study of a "rib tumor" discovered during a routine x-ray examination.

For several years the patient had experienced moderate pain in the right shoulder posteriorly that occurred particularly when he remained in the sitting position for any length of time. Occasionally he had to stop playing the piano because of this pain, which never seriously interfered with other activities, however. Four months before entry a routine chest x-ray film taken at his place of employment was found to show a "rib tumor." Review of a similar chest plate taken five years previously disclosed a smaller tumor in the same location. Two weeks before entry, the patient had an attack of "pleurisy" with sharp pain that was aggravated on inspiration and was most marked over the sixth costal rib on the right side. This episode lasted two days but did not interfere with any activity. There had been no cough, fever, chills, night sweats, fatigue, dyspnea, dysuria, flank pain or weight loss.

Physical examination was negative except for markedly impaired hearing in the left ear.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 100 diastolic.

Examination of the blood showed a white-cell count of 10,550 and a hemoglobin of 13.8 gm. The total protein was 7.0 gm., the phosphorus 2.6 mg. and the alkaline phosphatase 3.0 Bodansky units per 100 cc. A blood Hinton test was negative.

X-ray examination of the chest revealed localized cystic widening of the posterior medial aspect of the right second rib in the region of the rib angle. X-ray films of the pelvis, arms and hands were normal.

On the tenth hospital day an operation was performed.

Differential Diagnosis

Dr. Hugh F. Hare*: We have three sets of x-ray films showing the tumor. The first film reveals a lesion involving the second rib. There is only slight expansion of the rib; the lesion appears cystic and involves the cortex, but there is no evidence of any break through the cortex. Approximately 3 cm. of bone was involved at that time. The second film, which was taken five years

*Radiologist, Lahey Clinic.

later, shows an increase in the size of the tumor, as well as greater expansion of the rib than at the examination five years previously. In a third film taken a month after the second one, the lesion is practically unchanged, appearing multilocular, cystic and expansile.

The first problem that must be considered, if the diagnosis of rib tumor is correct, is whether the lesion was benign or malignant. A tumor that lasted for five years is quite likely to be benign, and we have sufficient evidence in the normal blood findings, the negative Hinton test and the normal blood protein, phosphorus and alkaline phosphatase that this was a localized process. We have further evidence that it was not malignant in that the lungs were clear. One possibility that should never be overlooked in a bone tumor, however, is a reticulum-cell sarcoma, which is a slowly growing lesion and is present a number of years before symptoms become apparent. I do not believe that we need consider plasmocytoma with a duration of five years, but we must consider an enchondroma or chondroma that may have become malignant. Against malignancy, however, is the fact that in this tumor we cannot see any break through the cortex. Therefore, I think that we can rule out a malignant lesion.

Of the benign lesions we must consider bone tumors and granulomas. I do not believe that we can make a differential diagnosis between granulomas and benign tumors from the x-ray films. The most frequent tumor that is found in this location is the giant-cell tumor. Out of a series of 400 cases described by Copeland and Geschickter* 2.5 per cent were giant-cell tumors of the rib. Another point in favor of bone tumor is that the patient was in the correct age group, being under thirty. Another possibility is bone cyst. The patient was older than the average patient with bone cyst, and the lesion is usually not multilocular; on the other hand, it was close to the epiphyseal margin, cysts generally occurring in such a location or in the metaphysis of the bone.

Proceeding to the granulomas, we should consider fibrous dysplasia, localized eosinophilic granuloma and ossifying fibroma, all of which can fairly well be included because of the fact that this was a multilocular lesion and had been present for a long time. It would not surprise me to find that this lesion belongs in the group of granulomas, because I have seen similar cases. The next possibility is a neurofibroma or von Recklinghausen tumor that had grown into the rib. These are extremely slowly growing processes. There is certain evidence in the x-ray films that could be so interpreted. The long-standing history, however, and the fact that the lesion was multilocular make me favor a giant-cell tumor.

*Geschickter, C. F., and Copeland, M. M. *Tumors of Bone*. 709 pp. New York: *American Journal of Cancer*, 1931.

DR. JAMES R. LINGLEY: What about the possibility of localized osteitis fibrosa cystica? Such a lesion is not too infrequent in the ribs. We have had several cases in the younger age group.

DR. HARE: I think that that is a good possibility, but I included it when I mentioned fibrous dysplasia. It is just a difference in terminology.

CLINICAL DIAGNOSIS

Benign rib tumor.

DR. HARE'S DIAGNOSIS

Benign giant-cell tumor.

ANATOMICAL DIAGNOSIS

Fibrous dysplasia of rib.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: The rib was resected, and a tumorlike expansion was found. On cutting into this it was seen to be filled with solid material, somewhat gritty in character. Microscopic examination showed marked thinning of the cortex. The marrow cavity was filled with connective tissue in which were many trabeculae of rather poorly formed bone — in other words, the characteristic picture of fibrous dysplasia. There was no cystic cavity that we could find; it was therefore not a true bone cyst.

The question comes up how cases of this type should be handled and how radical one should be in the treatment. Fibrous dysplasia is a chronic lesion that rarely if ever heals completely, but once the patient has passed beyond puberty, the extension is slow and usually stops completely. There is no record of a case of fibrous dysplasia that was followed by osteogenic sarcoma or other form of malignant tumor, so that there is no probability of harm to the patient if it is left untreated. When it occurs in the long bones there is the possibility of pathologic fracture. In the rib that is fairly unlikely, and I think that, if there had been any way in which the diagnosis could have been established, there was not much need for operating on this man. His disability was so slight that he was able to go through three years of military service.

Dr. Shipman, this was a patient of yours. Do you wish to add anything?

DR. THOMAS L. SHIPMAN: There is little that I can add. The second x-ray film was taken at a time when the patient was being re-employed after discharge from the service. The swelling of the rib five years previously had been missed, but I do not believe that we need apologize for that. We did spot the lesion in the rib in the later film and referred him to the hospital for treatment.

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COUNCIL MEETING

A stated meeting of the Council of the Massachusetts Medical Society was held on October 2, 1946.

On the recommendation of the Committee on Arrangements, the length of the annual meeting in 1947 was extended to cover three instead of the usual two and a half days. In this connection, acting on the recommendation of the Committee on Postwar Planning, the Council directed the Committee on Arrangements to provide for adequate discussion of some topic in medical economics.

Acting also on the recommendation of the Committee on Postwar Planning, the Council authorized the appointment of a special committee to study the medical resources of the Commonwealth, especially regarding how best to mobilize these resources in time of war or other disaster. This committee will act with a similar committee of the American Medical Association, which will direct its attention to the same subject on the national level.

In connection with the plan to provide medical care for veterans by civilian physicians, the Council agreed to differentiate the specialist and the general practitioner. A communication from the Veterans Bureau indicated that this was necessary if the plan was to go forward. Such a differentiation and the formula by which it will be arrived at were agreed on only for the purposes of the Veterans Administration. The Council likewise agreed that the fee schedule adopted by the Council on April 10, 1946, be reduced by 20 per cent when the services called for in the schedule are rendered by a general practitioner.

Two communications, one from the John Hancock Life Insurance Company and the other from the Liberty Mutual Insurance Company, were referred to the Committee on Public Relations for study by a subcommittee set up for this purpose. These communications dealt with the same subject—the merits of sickness-insurance plans sponsored by old-line insurance companies.

BAL—A CURE FOR HEAVY-METAL POISONING

The ill wind that blew chlorine gas from the German lines across no man's land in World War I and that started a race for the development of more and deadlier chemicals for use in warfare has now blown in some good. During the present war the search for antidotes to neutralize the action of arsenical vesicants, one of the most potent of which is lewisite, has resulted in the discovery of a therapeutic agent that is effective in counteracting the local and systemic effects of poisoning with arsenicals and with some other heavy metals. The agent is 2,3-mercaptopropanol and has been called BAL (British anti-lewisite). Announcement of the development and properties of this substance has been withheld until recently for reasons of security.

The discovery was made by Peters and his associates at Oxford and was based on earlier American work, which suggested that the toxic action of

arsenic on cells is due to the inactivation of thiol-containing enzymes. A search for other thiol compounds that would compete more effectively for the arsenic resulted in the development of BAL. Many different agencies and groups of workers in Great Britain and in the United States collaborated in these investigations throughout the latter part of the war, and the clinical studies in particular have continued since the close of hostilities. Announcements of the discovery of BAL, together with brief accounts of its pharmacologic and toxicologic properties and of the results of preliminary clinical trials in cases of arsenical and mercurial poisoning, have recently been made.[1, 2]

Experiments have shown that trivalent arsenicals exert their toxic action by combination with –SH groups of the activating protein of enzyme systems. Tissue respiration is interfered with by the action of the arsenicals on the large group of –SH enzymes essential for carbohydrate transformations and fat metabolism. The enzyme inhibitions produced by lewisite and arsenic can generally be prevented by BAL or by closely related dithiols. Furthermore, even when established, these inhibitions can be reversed by BAL and to a lesser extent by glutathione. In this reversal, BAL exhibits greater affinity for arsenic than do the thiols of the attacked tissue. Certain inhibitions produced by arsine, however, are actually enhanced by BAL, apparently because of the inherent toxicity of BAL itself for the enzyme system attacked by the arsine.

If trypanosomes or spermatozoa are subjected to lethal concentrations of arsenic they lose all motility and show early degenerative changes. If BAL is added, they regain their motility and normal cytologic appearance. The arsenic is actually removed from the damaged cells, as shown by an increase in the arsenic content of the supernatant fluid. BAL was found to be highly effective in the treatment of systemic poisoning in rabbits even when given several hours after the toxic dose of an arsenical.

It was also found that human beings could tolerate effective doses of BAL. Untoward reactions, however, were encountered when larger doses were used. An intramuscular dose of 5 mg. per kilogram of BAL in oil may cause a patient some discomfort in the form of lacrimation, burning of the lips, drying of the mouth and throat, generalized muscular aching, restlessness and nervousness, but no severe reactions were encountered and the effects of smaller doses were minimal. The untoward reactions to BAL seldom persisted for more than thirty minutes, and injections could be repeated at four-hour intervals.

BAL has been used in the treatment of the various arsenical reactions that occur during the course of the treatment of syphilis. These have included arsenical encephalitis, dermatitis, agranulocytosis, fever and jaundice. The early reports indicate a dramatic amelioration of symptoms and a marked reduction in the expected mortality. One interesting feature of BAL therapy in both experimental and clinical arsenic poisoning has been the extremely rapid increase in the excretion of arsenic that follows immediately after the injection of the antidote.

Extensive studies have also been made on the antidotal effects of BAL in experimental mercury poisoning, and the results have been striking. Apparently the interaction of one mol of BAL with one of bivalent mercury in vitro results in the formation of an insoluble compound, but the addition of another mol of BAL produces a substance that is difficult to dissociate but highly soluble. The efficacy of BAL in the treatment of mercurial poisoning is considered to be due to the rapid formation and excretion of the latter.

In the case of both mercurial and arsenical poisoning the efficacy of treatment is greatly decreased the longer it is delayed. Most dogs were protected, however, as long as two or three hours after intravenous injection and five hours after oral administration of mercuric chloride. When treatment was delayed for five hours after ingestion, in most fatal cases death was not associated with renal insufficiency but rather was the result of a severe gastroenteritis, which often was far advanced before the first dose of BAL was administered.

Clinical trials of BAL in human arsenical and mercurial poisoning were reported by Luetscher at the recent meeting of the American Society for Clinical Investigation.[3] Dermatitis was the most frequent form of arsenic intoxication and responded

to inunction or injection of BAL. The results in cases of hepatitis and blood dyscrasias were less striking. No deaths occurred in the 30 consecutive cases of arsenical intoxication that were treated with this drug. An increased urinary excretion of arsenic regularly followed the BAL treatment in cases of dermatitis, appearing each time that the course of treatment was repeated. This increase coincided with the appearance of BAL-like material in the urine. In cases of hepatitis, arsenic excretion was not regularly affected by the injections of BAL. Luetscher also reported apparent benefit from large doses of BAL in the treatment of 26 cases of mercurial poisoning. The mortality was about half the previous rate for the Johns Hopkins Hospital. The most striking features of BAL therapy were the prompt relief of even the most alarming symptoms, the rapidity with which the patients made a complete recovery and the low incidence of significant renal complications.

References

1. Waters, L. L., and Stock, C. BAL (British anti-lewisite). *Science* **102**:601-606, 1945.
2. Gilman, A. Therapeutic applications of chemical warfare agents. *Federation Proc.* **5**:292, 1946.
3. These data and others dealing with BAL are contained in a series of eleven papers by several authors appearing in the July, 1946, issue of the *Journal of Clinical Investigation*.

MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

CONRO — Arthur C. Conro, M.D., of Attleboro, died August 18. He was in his seventy-seventh year.

Dr. Conro received his degree from Chattanooga Medical College in 1901. He was a member of the New England Otological and Laryngological Society.

His widow and a son survive.

CROSBY — L. Marshall Crosby, M.D., of Wakefield, died October 24. He was in his seventieth year.

Dr. Crosby received his degree from Dalhousie University Faculty of Medicine, Halifax, Nova Scotia, in 1901. He was a former president of the Middlesex East District Medical Society and a fellow of the American Medical Association.

His widow survives.

O'DEA — Patrick J. O'Dea, M.D., of Fitchburg, died September 25. He was in his sixtieth year.

Dr. O'Dea received his degree from University of Vermont College of Medicine in 1912.

SULLIVAN — Arthur J. Sullivan, M.D., of Fall River, died August 6. He was in his fifty-seventh year.

Dr. Sullivan received his degree from Jefferson Medical College of Philadelphia in 1912.

A brother and a sister survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1946

Résumé

Diseases	September 1946	September 1945	Seven-Year Median
Anterior poliomyelitis	99	162	66
Chancroid	1	1	*
Chicken pox	114	90	105
Diphtheria	51	11	10
Dog bite	1078	924	923
Dysentery, bacillary	5	11	23
German measles	56	49	30
Gonorrhea	443	405	410
Granuloma inguinale	0	0	*
Lymphogranuloma venereum	1	0	*
Malaria	23	102	6
Measles	204	145	150
Meningitis, meningococcal	8	4	6
Meningitis, Pfeiffer-bacillus	1	0	0
Meningitis, pneumococcal	2	1	2†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	1	0	0†
Meningitis, other forms	3	2	1†
Meningitis, undetermined	1	3	4†
Mumps	101	194	194
Pneumonia, lobar	37	57	106
Salmonella infections	20	9	9
Scarlet fever	138	190	240
Syphilis	352	292	363
Tuberculosis, pulmonary	265	205	215
Tuberculosis, other forms	20	14	23
Typhoid fever	3	0	3
Undulant fever	1	2	2
Whooping cough	520	570	474

*Made reportable December, 1943.

†Four-year average.

Comment

Diseases reported at an incidence above the seven-year median included anterior poliomyelitis, chicken pox, diphtheria, German measles, measles, meningococcal meningitis, Salmonella infections and whooping cough.

Diseases reported below the median prevalence included bacillary dysentery, mumps, lobar pneumonia, scarlet fever and undulant fever.

Diphtheria continued to rise for the fifth consecutive month, the incidence being over five times the median prevalence. It is the highest for September in thirteen years.

Although above the median prevalence, poliomyelitis had an incidence of less than two thirds that of last year.

Undulant fever is reported at the lowest in seven years.

Lobar pneumonia has reached an all-time low.

Geographical Distribution of Certain Diseases

Anterior poliomyelitis was reported from: Amherst, 1; Barre, 1; Bellingham, 1; Boston, 9; Chicopee, 1; East Bridgewater, 1; Everett, 2; Falmouth, 1; Gardner, 1; Gloucester, 2; Greenfield, 1; Leverett, 1; Lowell, 2; Lunenburg, 1; Lynn, 2; Malden, 2; Medford, 2; Montague, 1; Natick, 1; Newton, 2; Northampton, 1; North Adams, 7; Northbridge, 1; Northfield, 2; Revere, 2; Shelburne, 2; Shrewsbury, 1; Southboro, 1; South Hadley, 1; Springfield, 1; Sudbury, 1; Sutton, 1; Walpole, 3; Waltham, 5; Watertown, 1; Wayland, 1; Webster, 1; Wellesley, 2; Weymouth, 1; Worcester, 29; total, 99.

Diphtheria was reported from: Boston, 23; Cambridge, 2; Everett, 1; Hanson, 1; Leominster, 1; Medfield, 1; New Bedford, 2; Somerville, 19; Worcester, 1; total, 51.

Dysentery, bacillary, was reported from: Boston, 2; Wrentham (State Hospital) 3; total, 5.

Lymphocytic choriomeningitis was reported from Agawam, 1; total, 1.

Malaria was reported from: Attleboro, 1; Boston, 4; Brockton, 2; Cambridge, 2; Dedham, 1; Hingham, 1; Lanesboro, 1; Lynn, 1; Newton, 3; Peabody, 1; Quincy, 1; Somerville, 1; Southboro, 1; Springfield, 1; Woburn, 1; Worcester, 1; total, 23.

Meningitis, meningococcal, was reported from: Adams, 1; Boston, 1; Chicopee, 1; Fitchburg, 1; Leominster, 1; Lowell, 1; Lynn, 1; Newburyport, 1; total, 8.

Meningitis, Pfeiffer-bacillus, was reported from: Haverhill, 1; total, 1.

Meningitis, pneumococcal, was reported from: Chicopee, 1; Mansfield, 1; total, 2.

Meningitis, streptococcal, was reported from Cambridge, 1; total, 1.

Meningitis, other forms, was reported from: Boston, 2; total, 2.

Meningitis undetermined, was reported from: Revere, 1; total, 1.

Salmonella infections were reported from: Boston, 1; Brewster, 1; Brockton, 4; Holyoke, 1; Lynn, 1; Methuen, 3; Newton, 1; Northfield, 3; Salem, 1; Swampscott, 1; Topsfield, 1; Watertown, 1; Worcester, 1; total, 20.

Septic sore throat was reported from: Boston, 2; Lynn, 1; Williamstown, 2; total, 5.

Tetanus was reported from: Duxbury, 1; total, 1.

Trichinosis was reported from: Boston, 1; total, 1.

Typhoid fever was reported from: Boston, 1; Chelsea, 1; Holyoke, 1; total, 3.

Typhus fever was reported from: Boston, 1; total, 1.

Undulant fever was reported from: New Bedford, 1; total, 1.

MISCELLANY

CAMPAIGN TO COMBAT HEART DISEASE

The initiation of a nationwide program of public education and information on diseases of the heart was recently announced by officials of the American Heart Association, Incorporated.

The program, according to Dr. Howard F. West, of Los Angeles, president of the association, will have as its prime purpose "the dissemination of educational information to the public in a broad effort to retard the rapid increase of heart disease throughout the nation.

"Fatalities ascribed to diseases of the heart," Dr. West said, "are greater than the total of the next five leading causes of death. It is essential, therefore, that the public know more about the significance of blood pressure, infections, obesity, rheumatic fever and other factors which contribute to various types of heart disease."

It is estimated that there are more than 4,000,000 people in the United States today who have heart disease. Diseases of the heart and blood vessels, including cerebral hemorrhage, accounted for 575,000 deaths in 1944. Fatalities from the five other leading causes in 1944 were as follows: cancer, 171,000; accidental deaths, 95,000; nephritis, 92,000; pneumonia, 64,000; and tuberculosis, 55,000. In addition to accounting for more fatalities than these five causes combined, heart disease is responsible for an annual loss of more than 100,000,000 work days.

Officials of the American Heart Association state that the association's program will call for emphasis on educational work with schools, parent-teacher associations and other groups concerned with children because of the importance of rheumatic fever and heart disease. According to recent surveys, this scourge of children causes more than five times as many deaths as the combined total of deaths from infantile paralysis, scarlet fever, diphtheria, measles, meningitis and whooping cough. It is a serious disease among adults, too, as illustrated by the estimated 40,000 veterans who acquired the disease during their recent military service.

The war forcibly dramatized the need for a national health program designed to retard the increase in heart disease cases. An estimated 10 per cent of the men rejected by Selective Service were disqualified because of cardiovascular diseases. In a survey of a special sampling of 5000 rejectees for cardiovascular diseases in five major cities, — Chicago, New York, Boston, Philadelphia and San Francisco, — 50 per cent had been disqualified because of rheumatic heart disease. The second greatest cause of rejection due to cardiovascular diseases was hypertension, which accounted for nearly 26 per cent of the disqualifications.

The educational campaign of the American Heart Association will reach its climax during National Heart Week, to begin on February 9, 1947, which includes St. Valentine's Day. It is expected that all branches of medicine, pharmacy, insurance, industry and many other groups interested in health and public welfare will co-operate fully.

Supporting groups will include the following national organizations, which comprise the American Council on Rheumatic Fever of the American Heart Association: American Academy of Pediatrics, American Association of Medical Social Workers, American College of Physicians, American Hospital Association, American Medical Association, American Nurses Association, American Public Health Association, American Rheumatism Association, American School Health Association, National Organization for Public Health Nursing and National Society for Crippled Children and Adults. The collaboration of the United States Public Health Service, National Tuberculosis Association and others is expected.

NOTICES

ANNOUNCEMENTS

Dr. Joseph Factor announces the removal of his office to 475 Commonwealth Avenue, Boston.

Dr. James S. Mansfield, having returned from military service, is resuming the practice of internal medicine at 12 Bay State Road, Boston.

BOSTON GASTROENTEROLOGICAL SOCIETY

The next meeting of the Boston Gastroenterological Society will be held in the New Cheever Amphitheater, Dowling Building, Boston City Hospital, on Wednesday, November 13, at 12 noon. Dr. Frank H. Lahey will speak on the subject "The Management of Biliary-Tract Disease."

NEW ENGLAND ROENTGEN RAY SOCIETY

The next meeting of the New England Roentgen Ray Society will be held at the Hotel Beaconsfield on Friday, November 15. The x-ray conference at 4:30 p.m. will be devoted to therapy of benign lesions. At 8:00 p.m., Dr. Maurice Lenz will speak on the subject "Cancer of the Breast."

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 19, at twelve noon. Dr. Norman H. Boyer will speak on the subject "Some Clinical Aspects of Coronary Artery Disease." Dr. Samuel Grossman will preside.

Physicians are cordially invited to attend.

AMERICAN MEDICAL ASSOCIATION

At the Centennial Session of the American Medical Association, to be held in Atlantic City, June 9 to 13, 1947, the Scientific Exhibit will include both the history of medicine during the past century and the latest developments of medical science.

Application blanks for space are now available. All applicants must fill out the regular form. Applications close on January 13, 1947, after which time the Committee on Scientific Exhibit will make its decision and notify the applicants.

Application blanks for space should be procured as soon as possible. They are available from the Director, Scientific Exhibit, American Medical Association, 535 North Dearborn Street, Chicago 10, Illinois.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 14

FRIDAY, NOVEMBER 15

*9:00-10:00 a.m. Carcinoma *in situ*. Dr. Tracy B. Mallory. Joseph H. Pratt Diagnostic Hospital.

*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, NOVEMBER 18

*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, NOVEMBER 19

*12:15-1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, NOVEMBER 20

*9:00-10:00 a.m. Certain Peculiarities of Brain Metabolism. Dr. David Rapport. Joseph H. Pratt Diagnostic Hospital.

*10:30-11:30 a.m. Medical Clinic. Isolation Building Amphitheater. Children's Hospital.

*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

(*Notices continued on page xiv*)